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Severe Acute Respiratory Syndrome

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On the Cover:
Liu Sung-nien (1174-1224),
Sung Dynasty. Lohan (1207)
National Palace Museum,
Taiwan, Republic of China.
Hanging scroll, ink and colors on silk
(117 cm x 55.8 cm)

About the Cover, pg. 387

Commentary

SARS Origins

SARS Epidemiology

SARS Transmission

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Wresting SARS from Uncertainty

Jairam R. Lingappa,* L. Clifford McDonald,* Patricia Simone,* and Umesh D. Parashar*

In early March 2003, Carlo Urbani, a World Health Organization (WHO) epidemiologist stationed in Vietnam, alerted the global health community to the high transmissibility and lethality associated with an apparently new respiratory disease. This disease, now called severe acute respiratory syndrome (SARS), is believed to have emerged in China in November 2002 and progressed to a global health threat by the spring of 2003 (1–3). On March 15, 2003, with clusters of SARS cases being reported from China, Hong Kong, Vietnam, Singapore, and Canada, WHO issued a global travel alert. At that point, the international health community faced a potential pandemic for which there were no identified causal agent, no diagnostic laboratory assays, no defined properties or risk factors for transmission, no infection-control practices of proven efficacy, and no known treatment or prevention measures. Given that setting, the declaration on July 5 that SARS had been contained (in less than 4 months after its initial recognition), represented a remarkable achievement for a truly extraordinary international public health effort.

However, the SARS outbreak was not contained before it had had a substantial impact: 8,098 cases involving 774 deaths were attributed to SARS (4) (the original WHO case definitions [5] were revised during the outbreak to those shown in the Table); fear of contagion was rife in many communities, especially among healthcare workers; and billions of dollars had been lost in the airline and tourism industries, resulting in bankruptcies of airlines and other businesses. However, the SARS public health response effort was equally important: the world's scientific, clinical, and public health communities had successfully instituted sensitive surveillance for the disease; isolation and infection-control practices—with intensive contact tracing and community containment, including quarantine—were effective in limiting continued spread in most cases; and the causative agent and diagnostic assays for detecting the disease were identified.

Now, nearly 1 year after the world first faced this infectious disease challenge, the public health community is equipped with a broader understanding of the agent, its pathophysiology, clinical signs and symptoms, risk factors for transmission, and public health measures that can successfully contain the disease. The breadth of this understanding and international scope of the outbreak response are reflected in the range of manuscript topics in this issue

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Dr. McDonald is a medical epidemiologist in the Division of Healthcare Quality Promotion, CDC, which has primary responsibility for public health response activities in healthcare settings. During the SARS outbreak, he was a member of the Clinical and Infection Control Team, working in the Emergency Operations Center activated for SARS; he also led the CDC SARS Investigation Team to Toronto during both phases of the outbreak there.

Dr. Simone is the associate director for science in the Division of Global Migration and Quarantine, CDC. She is responsible for the scientific activities of that division, whose missions are to decrease illness and death from infectious diseases among mobile populations (immigrants, refugees, migrant workers, and international travelers) crossing international borders destined for the United States and to decrease the risk for importation and spread of infectious diseases via humans, animals, and cargo. She is an expert on tuberculosis and serves as the SARS team leader for travel-related issues.

Dr. Parashar is the lead medical epidemiologist for the CDC SARS Task Force, Division of Viral and Rickettsial Diseases, which has overall responsibility to develop, oversee, coordinate, and implement CDC's SARS program activities. Dr. Parashar was a member of the World Health Organization team that investigated the SARS epidemic in Hong Kong and later led the surveillance team at CDC during the response to the SARS outbreak in the United States.

Table. World Health Organization SARS case definitions

Suspected case-patient: a person presenting after November 1, 2002,[b] with a history of (ALL THREE):
1. High fever (>38°C) AND
2. Cough or breathing difficulty, AND
3. One or more of the following exposures during the 10 days before onset of symptoms:
   - close contact[c] with a person who is a suspected or probable SARS case-patient
   - history of travel to an area with recent local transmission of SARS
   - residing in an area with recent local transmission of SARS

Probable case-patient: a suspected case-patient with:
1. Radiographic evidence of infiltrates consistent with pneumonia or respiratory distress syndrome (RDS) on chest x-ray OR
2. Consistent respiratory illness that is positive for SARS coronavirus by one or more assays, OR
3. Autopsy findings consistent with the pathology of RDS without an identifiable cause

[a]Revised May 1, 2003 (6). SARS, severe acute respiratory syndrome.
[b]The surveillance period begins on November 1, 2002, to capture cases of atypical pneumonia in China now recognized as SARS. International transmission of SARS was first reported in March 2003 for cases with onset in February 2003.
[c]A close contact is someone who cared for, lived with, or had direct contact with respiratory secretions or body fluids of a suspected or probable SARS case-patient.

of Emerging Infectious Diseases. Herein we review some of the salient features of the biology and epidemiology of SARS while underscoring some of the remaining unanswered questions.

The origins of the SARS-associated coronavirus (SARS-CoV) remain unclear; however, data suggest that the outbreak may have been preceded by transmission of this or a related virus from animals to humans. SARS-CoV has now been shown to infect (although not necessarily be transmissible through) other animals, including macaques (7), ferrets and cats (8), and pigs and chickens (9), although none of these animals are known to act as natural amplifying hosts for the virus. Antibodies to SARS-CoV have been identified in animal handlers (10), and a SARS-like coronavirus has been identified in palm civets and other animals indigenous to Guangdong Province, where SARS likely originated (11). Furthermore, serologic studies in Hong Kong suggest that SARS-like viruses may have circulated in human populations before the 2002–2003 outbreak (12).

As the SARS outbreak unfolded in Vietnam, Singapore, and Hong Kong, hospital workers stood out as a critical high-risk group. We now know that in many locations the SARS outbreak began with ill travelers coming from other SARS-affected areas (13). For many affected areas with low case numbers, such as the United States (where only eight cases were laboratory-confirmed [14–16]), SARS remained a travel-associated illness only, with no hospital or community transmission (14,17,18). However, healthcare settings played a key role in amplifying disease outbreaks (19). In locations such as Singapore, Canada, and Vietnam, disease was transmitted to many hospital workers by ill travelers or contacts of ill travelers, but in these locations, disease was successfully contained within hospitals. If the disease was not rapidly controlled in healthcare settings, as occurred in China, Taiwan, and Hong Kong, spread into the community occurred, resulting in extensive disease transmission (20,21) (Figure).

Most SARS patients had a clear history of exposure to other SARS patients or SARS-affected areas. Even in China, despite its extensive community transmission, intensive investigation successfully linked many cases previously classified as "unlinked" to high-risk exposures to SARS patients in fever clinics and other locations (20). Older persons were at greatest risk for severe disease, with fatality rates of nearly 50% in persons >60 years of age, whereas, for unclear reasons, fewer children were affected; those that were had lower morbidity and mortality (22–24).

A critical question has been whether SARS-CoV is transmitted through large droplets or on fomites, as occurs with respiratory syncytial virus, variola, and mycoplasma, or through aerosols, as occurs with measles and varicella. We now know that large droplets are likely the primary mode of transmission; however, in some circumstances, clusters suggestive of aerosol transmission have been described (19,25,26). Transmission appears to be heterogeneous. Most probable SARS cases were associated with little or no transmission. Although low transmission most commonly occurs in association with appropriate infection-control practices (27), cases have also been documented with no transmission despite ample exposure opportunities (17,18,28–30). Transmission in hospital settings has been clearly documented (25,31–33). Hospital transmission, along with infrequent "superspreading events," involving transmission from one case to many secondary cases, was critical to propagating the outbreak (19,25,26,34). Limited risk factors for superspreading events have been identified, including more severe illness, slightly older age, and an increased number of secondary contacts (34); however, further epidemiologic, virologic, and host-factor studies are needed to fully elucidate the risk factors that underlie SARS-CoV transmission.

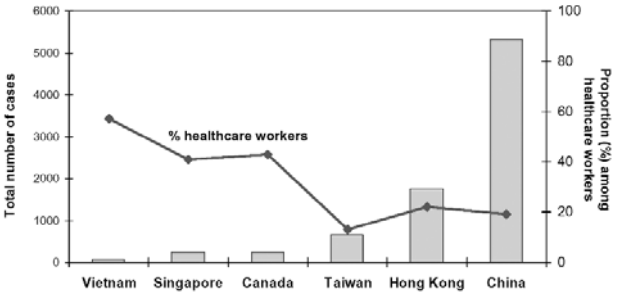

Figure. Cumulative cases of severe acute respiratory syndrome and proportion among healthcare workers by geographic region, November 1, 2002–July 31, 2003.

Fortunately, the outbreak demonstrated that SARS-CoV transmission can be effectively contained by strict adherence to infection-control practices. The use of N95 respirators or surgical masks was found to effectively reduce transmission in hospitals (31,33); this protective capacity of masks also has been shown for community transmission (20). Premature relaxation of infection-control measures in some SARS-affected areas had profound implications (35). Studies have demonstrated the importance of preexposure infection-control training and consistent use of masks, gowns, gloves, and eye protection (36).

Serologic and nucleic acid assays to detect SARS-CoV infection and virus, respectively, were developed early in the outbreak investigation (37–39). Comparative studies have now confirmed the sensitivity and specificity of enzyme-linked immunosorbent assays for detecting SARS antibodies (40) and of multitargeted real-time reverse transcription–polymerase chain reaction (RT-PCR) assays for detecting SARS-CoV infection (41,42). Although these assays are sensitive for detecting antibody and viral RNA, they have provided limited help in diagnosing SARS early in the course of disease (15,16,43,44). However, since the SARS clinical case definition is nonspecific, capturing respiratory illness caused by other pathogens (e.g., *Mycoplasma pneumoniae* and influenza) (14), laboratory confirmation of SARS-CoV infection is of particular importance for focusing control efforts during an outbreak and for refining SARS clinical studies. Such studies have shown that less than one third of patients initially have respiratory symptoms and, although abnormal findings on chest radiographs are universal for SARS patients, radiographic changes may not be discerned until 7 to 10 days after illness onset (45,46).

Diagnostic assays have also been important in describing the natural history of SARS infection and the associated immune response (29,43,47). Seroconversion within 28 days after symptom onset has been documented in 92% to 100% of probable SARS cases. Furthermore, during the first 4 days of illness, SARS-CoV is detectable by RT-PCR in respiratory secretions from less than half of the case-patients. Virus is subsequently detected in stool, and peak levels in both respiratory and stool specimens are found by day 11–12 of illness; virus can persist in stool for weeks thereafter (29,42,43,47). These studies underscore the continued need for SARS-CoV laboratory assays that are sensitive early in the disease course to support rapid clinical and infection-control decision-making.

The possibility remains that SARS may reemerge from unidentified animal reservoirs or from persistently infected humans. Current planning efforts for response to a future SARS resurgence rely upon vigilant application of clinical and epidemiologic criteria to evaluate cases of febrile illness (48). A bold and swift public health response to this disease must be applied with fairness and in a manner that preserves dignity for all. Response to any future resurgence of SARS will be aided by the body of knowledge about the infection that now exists and by the international experience in successfully containing the first SARS outbreak.

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The Impressive and Rapidly Expanding Knowledge Base on SARS

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Three days after issuing a global alert (1) about cases of atypical pneumonia in several countries in southeast Asia, the World Health Organization (WHO) introduced the term SARS to the world's lexicon (2). Familiarity with the newly coined acronym for "severe acute respiratory syndrome" was immediate, fueled by fear and by virtually continuous coverage by the media.[1] This intense reaction and scrutiny would generate multifaceted outcomes, enabling widespread collaboration and communication to help curb the tragic health consequences while wreaking economic, social, and even political havoc in many areas.

With similar speed, the clinical, public health, and research communities worldwide mounted an aggressive response to the new disease. Under the leadership of WHO, members of normally competitive groups worked together, often communicating several times a day, to acquire and share knowledge to stop the spread of disease. Events unfolded rapidly, requiring implementation of traditional control measures while generating in a matter of weeks an impressive body of knowledge about an unknown member of the coronavirus family. Scientific journals played a major role in this endeavor, expediting online publication of peer-reviewed data and other evolving information.

The articles in this special SARS issue of *Emerging Infectious Diseases* are representative of this sustained involvement and commitment, with respect to both scope of authorship and range of topics. This diversity also illustrates the substantial contributions of many disciplines to the growing knowledge base on SARS. The articles describe findings from clinical and epidemiologic investigations, laboratory research, and social and behavioral studies, and discuss lessons learned both locally and globally.

More than a decade ago, the Institute of Medicine (IOM) issued a report (3) on the continued risks of infectious diseases, outlining factors contributing to the increased emergence of such threats in a globalized era and steps that should be taken to adequately address them. Ironically, within a week of WHO's unprecedented global alert (1), the IOM released an updated report (4) on emerging microbial threats, expanding on the severity and scope of the problem. The new report describes issues affecting disease emergence such as international travel and commerce, environmental changes, poverty and inequity, and the adaptability of microbes, and strongly emphasizes the need for increased surveillance and response capacity on a global level. The emergence of SARS reinforced the urgency of the situation, serving as an impetus for fundamental changes in the way the global health community interacts and bringing the message home to policymakers and the public.

Maintaining this motivation for change is essential. Efforts are needed to strengthen health systems nationally and internationally and to encourage and strengthen multidisciplinary collaborations among clinical, public health, research, and veterinary specialists worldwide. In addition, while technologic advances have increased access to and sharing of new information in unprecedented ways, we must recognize that the most vulnerable populations often do not have access to such information and look for new ways to convey essential health messages. Finally, as experience has so clearly demonstrated, vigilance for the unusual on the part of clinicians, laboratory workers, public health officials, and others, including the public, will continue to be a critical initial step in recognizing and responding to future emerging global microbial threats.

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[1]As of December 31, 2003, a National Library of Medicine PubMed search using the term SARS produced >1,500 results; a popular Internet search engine produced more than 5.3 million.

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Global Surveillance, National Surveillance, and SARS

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The international response to the severe acute respiratory syndrome (SARS) outbreak, from March to July 2003, tested the assumption that a new and emerging infection–one that had not yet demonstrated its full epidemiologic potential but was spreading from person to person and continent to continent–could be prevented from becoming endemic. Within 4 months after the first global alert about the new disease, all known chains of transmission had been interrupted in an outbreak that affected 27 countries on all continents. Most public health experts and scientists believe that the question of whether SARS has become endemic, or will re-emerge, can only be answered after at least 12 months of postoutbreak surveillance. The SARS experience, however, made one lesson clear early in its course: inadequate surveillance and response capacity in a single country can endanger national populations and the public health security of the entire world. As long as national capacities are weak, international mechanisms for outbreak alert and response will be needed as a global safety net that protects other countries when one nation's surveillance and response systems fail.

During the last decade of the 20th century, several outbreaks, including cholera in Latin America, pneumonic plague in India, and Ebola hemorrhagic fever in the Democratic Republic of the Congo, caused great international concern (1–3). These events demonstrated the consequences that delayed national recognition and response to outbreaks could have: illness and death of national populations including health workers, potential spread to other countries, and significant disruptions of travel and trade. These outbreaks also emphasized the need for a global surveillance and response mechanism. The Global Outbreak Alert and Response Network (GOARN), set up in 1997 and formalized in 2000, was one major response to this need (World Health Organization [WHO], unpub. data and 4). Though the network, which now has over 120 partners throughout the world, currently identifies and responds to more than 50 outbreaks in developing countries each year, the SARS outbreak was the first time that GOARN identified and responded to an outbreak that was rapidly spreading internationally.

One of the partners in GOARN is the WHO Global Influenza Surveillance Network, which was established in 1947 to guide the annual composition of vaccines and provide an early alert to variants that might signal the start of a pandemic of rapidly evolving influenza viruses. This network was placed on alert in late November, when the Canadian Global Public Health Intelligence Network (GPHIN), also a partner in GOARN, picked up media reports of an influenza outbreak in mainland China (5). Simultaneously, another GOARN partner, the U.S. Global Emerging Infections Surveillance and Response System (GEIS), became aware of similar reports about a severe outbreak, with influenza B the suspected cause, in Beijing and Guangzhou. As GOARN continued to receive reports about influenza outbreaks in China, WHO requested information from Chinese authorities on December 5 and 11. On December 12, WHO received a detailed report on data collected at Chinese influenza surveillance sites, indicating that investigation of 23 influenza virus isolates had confirmed type B strains in all but one and that the number of cases was consistent with the seasonal pattern in previous years. The information was reassuring and an indication that the influenza surveillance system was working well.

Although information is incomplete, retrospective case identification by Chinese and GOARN epidemiologists since May 2003 suggests that two respiratory disease outbreaks occurred in Guangdong Province in late November 2002: influenza and what now appears to have been a first wave of SARS cases—an atypical pneumonia that was characterized by small, seemingly unrelated clusters of cases scattered over several municipalities in Guangdong, with low-level transmission to healthcare workers (6). This first wave of atypical pneumonia appears to have continued until a second wave of disease with amplified

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transmission to health workers began occurring during the first 10 days of February (WHO, unpub. data). On February 10, 2003, the WHO office in Beijing received an email message describing an infectious disease in Guangdong Province said to have caused more than 100 deaths. On February 11, the Guangzhou Bureau of Health reported to the press more than 100 cases of a respiratory atypical pneumonia outbreak that had been spreading in the city for more than 1 month. That same day, the Chinese Ministry of Health in Beijing officially reported to WHO 300 cases and 5 deaths in an outbreak of acute respiratory syndrome, and the next day reported that the outbreak dated back to November 16, 2002, that influenza virus had not yet been isolated, and that the outbreak was coming under control (7).

When the reports of a severe respiratory disease were received by WHO on February 11, 2003, a new strain of influenza virus was the most feared potential cause, and the WHO Global Influenza Network was again alerted. Concern grew on February 20, when the network received reports from Hong Kong authorities confirming the detection of A(H5N1) avian influenza virus in two persons, and WHO activated its influenza pandemic preparedness plans (8).

During that same week, laboratories of the WHO Global Influenza Surveillance Network began analyzing specimens from a patient with severe atypical pneumonia hospitalized in Hanoi after travel to Hong Kong. Concurrently, GOARN response teams in Vietnam and Hong Kong began collecting clinical and epidemiologic information about the patient and a growing number of others with similar symptoms. As more specimens entered the network laboratories, influenza viruses were ruled out as the causative agent. WHO made its first global alert on March 12, followed by a second, on March 15, when more than 150 suspected new cases had been reported from several geographic areas, including Hong Kong, Singapore, Vietnam and Canada (9,10). With the second alert, WHO provided a case definition and name, thus beginning a coordinated global outbreak response that brought heightened vigilance everywhere and intense control efforts. GOARN linked some of the world's best laboratory scientists, clinicians, and epidemiologists electronically, in virtual networks that provided rapid knowledge about the causative agent, mode of transmission, and other epidemiologic features (11). This real-time information made it possible for WHO to provide specific guidance to health workers on clinical management and protective measures to prevent further nosocomial spread. It also made possible recommendations to international travelers to curtail international spread. Recommendations were at first nonspecific, urging international travelers to have a high level of suspicion if they had traveled to or from areas where the outbreak was occurring. But as more information became available, airports were asked to screen passengers for history of contact with SARS and for persons with current illness that fit the SARS case definition. Finally, when these recommendations did not completely stop international spread, passengers themselves were asked to avoid travel to areas where contact tracing was unable to link all cases to known chains of transmission (12). Within 4 months, transmission of SARS had been interrupted at all sites, and on July 5, 2003, the SARS outbreak was declared contained (13).

As many times occurs with emerging and reemerging infectious diseases, national surveillance mechanisms failed to identify and respond to the emerging outbreak of SARS early enough to prevent its toll of sickness, death, and international spread (14). In May 2003, ministers of health from the 192 member countries of WHO expressed their deep concern about the impact of SARS and its implications for future outbreaks, which were considered inevitable. In two resolutions, they called for increased national capacity development for surveillance and response and endorsed the ways in which GOARN obtained information about SARS and supported containment efforts (15,16). The resolutions stressed the need for countries to give more attention, with WHO support, to the strengthening of national surveillance and response capacity, and encouraged WHO to continue to strengthen GOARN, its safety net for global alert and response. As SARS so amply demonstrated, protection against the threat of emerging and epidemic-prone diseases requires strong defense systems at national as well as international levels.

Dr. Heymann is a medical epidemiologist who began his career in India with the smallpox eradication program. After completing the Epidemic Intelligence Service, Dr. Heymann spent 13 years working for CDC in sub-Saharan Africa in infectious diseases that range from Ebola, yaws, and yellow fever to the routine childhood immunizable diseases and malaria. On joining the World Health Organization, Dr. Heymann worked with the AIDS program, then set up and directed the Department of Emerging and other Infectious Diseases before becoming executive director for the Communicable Disease program, followed by his present assignment as the representative of the director general, heading the Polio Eradication Initiative.

Dr. Rodier is currently the director, Department of Communicable Disease Surveillance and Response, World Health Organization. His main professional experience includes the development of new approaches for communicable disease surveillance and response at national and global levels, and comprehensive field experience in epidemic response, particularly in viral hemorrhagic fever.

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SARS-related Virus Predating SARS Outbreak, Hong Kong

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Using immunofluorescence and neutralization assays, we detected antibodies to human severe acute respiratory syndrome–associated coronavirus (SARS-CoV) and/or animal SARS-CoV–like virus in 17 (1.8%) of 938 adults recruited in 2001. This finding suggests that a small proportion of healthy persons in Hong Kong had been exposed to SARS-related viruses at least 2 years before the recent SARS outbreak.

A novel coronavirus has been identified as the cause of the 2003 global outbreak of severe acute respiratory syndrome (SARS) (1–5). Genetic analysis and epidemiologic studies suggest that SARS coronavirus (CoV) was introduced into humans not long ago. Recently, SARS-CoV–like viruses were isolated in Himalayan palm civets and racoon dogs in a retail live animal market in Guangdong Province, southern China (6), and some of the animals tested had antibodies to SARS-CoV–like virus. Phylogenetic analysis showed that the SARS-CoV–like animal viruses were closely related to the viruses found in humans. Serologic surveillance demonstrated that, in the same market, approximately 40% of wild animal traders and 20% of animal slaughterers had antibodies to SARS-CoV or SARS-CoV–like animal virus, but none of them had had SARS-like symptoms in the past 6 months. These investigations raised questions about whether the presence of the animal SARS-CoV–like virus in the market was an isolated event or if this virus had been prevalent in the human population in southern China before the SARS outbreak. A retrospective serologic study was conducted to address these questions.

The Study

Serum samples collected in May 2001 from 938 healthy Chinese adults in Hong Kong and 48 confirmed SARS patients diagnosed in February and March 2003 in Guangdong were studied. All serum samples were aliquoted and stored at −20°C. The healthy adults were totally asymptomatic persons randomly recruited after a telephone interview concerning hepatitis B virus. The signs and symptoms of the SARS patients met the World Health Organization's definition for surveillance, and SARS-CoV infection had been confirmed virologically.

All serum samples were heated at 56°C for 30 minutes. Specific antibodies for SARS-CoV and SARS-CoV–like virus were tested by using immunofluorescence (IF) assay at 1:10 dilution on FRhK-4 cells infected with either a human SARS-CoV strain (GZ50) (5) or an animal SARS-CoV–like virus (SZ16) (6), as reported (1). For sera positive for anti–SARS-CoV or anti–SARS-CoV–like virus, the antibody titer was further determined by serial titration. The IF-positive serum samples were serially diluted from 1:20 to 1:640 and then mixed with 100 50% tissue culture infective dose $(TCID)_{50}$ of the representative human or animal virus strains for a serum neutralization assay. After incubation for 1 hour at 37°C, the mixture was inoculated in triplicate onto 96-well plates of FRhK-4 cell cultures. The results were determined after 3-day incubation at 37°C.

Seventeen (1.8%) archived samples from healthy adults showed IF antibodies against the human virus, animal virus, or both (titer range 1:20 to 1:1,280) and were confirmed by serum neutralization assay. An additional six samples were IF-antibody positive at a 1:10 dilution to either animal or human viruses, but they were negative in neutralization assay and were treated as negative. The positive rate was highest in the group ages 51 to 60 years and appeared to be more prevalent in female (13/561, 2.3%) than male patients (4/377, 1.1%) (Table). Of the 17 seropositive serum samples, 10 were from housewives, retired, or unemployed persons; 6 were from clerks, unskilled workers, or students; and one was from a professional (Table). Most of the seropositive persons (13/17) had a higher IF or neutralization antibody titer to the animal virus than the human virus (Figure). By contrast, the control group, comprising convalescent-phase sera from

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Table. Distribution of age, gender, and occupation of SARS-CoV–seropositive adults recruited in 2001

Age (y)	No. of positive/total (%)	No. of positive/total in males (%)	No. of positive/total in females (%)	Occupation groups[b]	No. of positive/total (%)
17–30	2/162 (1.2)	0/73 (0)	2/89 (2.2)	1	10/367 (2.7)
31–40	3/236 (1.3)	0/93 (0)	3/143 (2.1)	2	5/235 (2.1)
41–50	6/283 (2.1)	1/100 (1.0)	5/183 (2.7)	3	2/221 (0.9)
51–60	4/150 (2.7)	3/57 (5.3)	1/93 (1.1)	4	0/110 (0)
>60	2/107 (1.9)	0/55 (0)	2/52 (3.8)	5	0/5 (0)
Total	17/938 (1.8)	4/378 (1.1)	13/560 (2.3)		17/938 (1.8)

[a]SARS-CoV, severe acute respiratory syndrome–associated coronavirus.
[b]Group 1: Housewives (235), retired persons (96), and unemployed persons (36); Group 2: clerks (141), students (40), and associate professionals (54); group 3: service workers (47), craft-related workers (41), machine operators (56), and unskilled workers (77); group 4: managers and administrators professionals (33), professionals (35), civil servants (9), and sales persons (33); group 5: undefined.

48 confirmed SARS patients recruited from hospitals in Guangdong, all showed positive antibody results for both human SARS-CoV and animal SARS-CoV–like viruses, but they invariably exhibited higher IF and neutralization antibody levels against the human virus than the animal virus (Figure).

Conclusions

While the exposure history and symptoms of study participants were unavailable for assessment, our results suggest that a small portion of Hong Kong adults had acquired a SARS-CoV–related virus infection at least 2 years before the 2003 SARS outbreak. Cross-reactivity of the antibody to human SARS-CoV and the animal SARS-CoV–like virus must have occurred, in view of the marked similarity between the two viruses. Recently, we reported that the very similar sequences differed only by 60 to 80 nt, including an additional 29 nt in the animal virus (6). We speculate that the viruses that affected the 17 healthy persons >2 years ago were antigenically closer to the recently isolated animal SARS-CoV–like virus than human SARS-CoV, but interspecies transmission from animal to human was probably inefficient as the viruses might not have adapted in the new host. This hypothesis

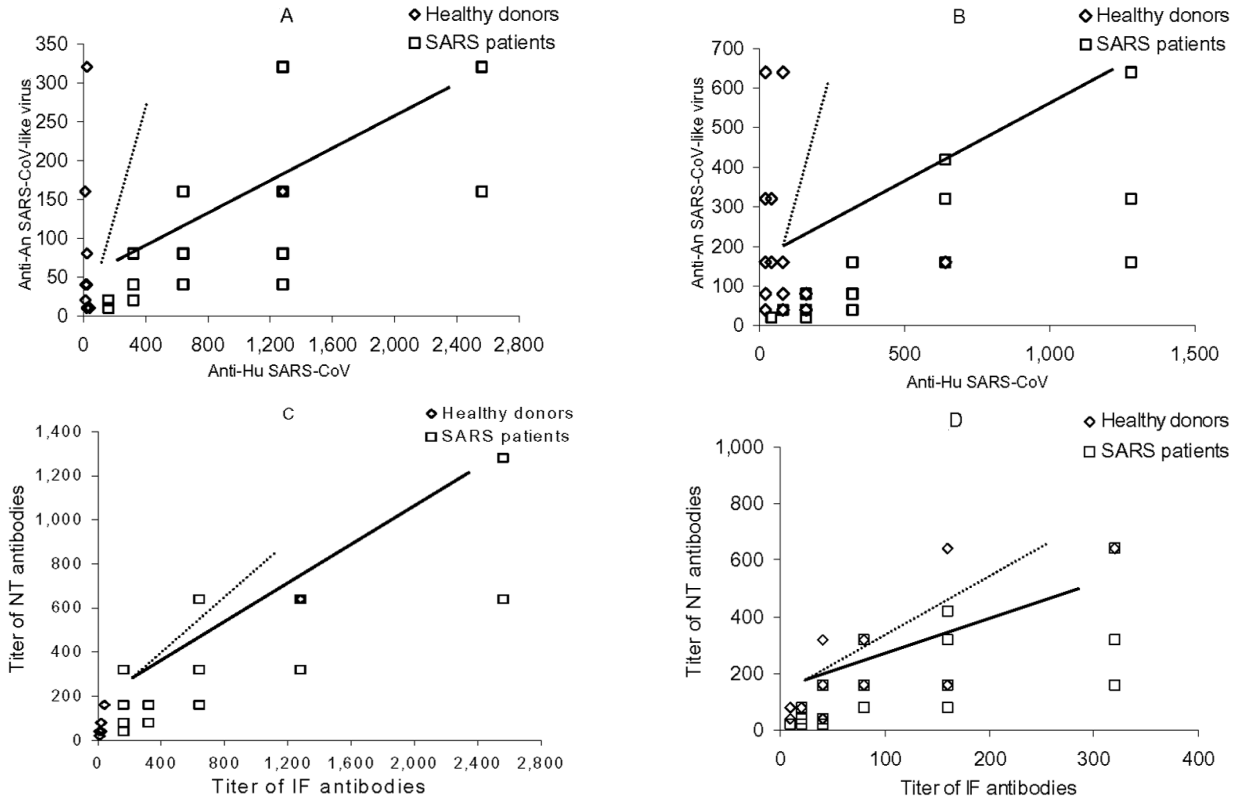

Figure. Correlation between antibodies against human severe acute respiratory syndrome cornonavirus (SARS-CoV) (anti-Hu SARS-CoV) and animal (anti-An) SARS-CoV–like virus in seropositive healthy adults recruited in 2001 (dotted line) and in patients with SARS in 2003 (thick line) by an immunofluorescence (A) and a neutralization (B) assay; and between neutralizing (NT) and immunofluorescence (IF) antibodies against Hu SARS-CoV (C) and a SARS-CoV–like virus (D).

would explain why only a few persons became infected and why they were likely to be asymptomatic. Avian influenza is another example of a virus appearing first in animals before causing a human disease. While approximately 3%–10% of healthy persons who were in close contact with farm or market chicken or fowls showed positive antibody to avian influenza viruses at the time of the H5N1 outbreak in humans in 1997, none of them had symptoms of influenza (7).

Although human SARS-CoV and animal SARS-CoV–like viruses are related to the three families of coronaviruses that cause respiratory and gastrointestinal diseases in animals, phylogenetic analysis has shown that they are different enough to make up their own, fourth group. The number of members in this new group is not clear. Important factors in the emergence of novel infectious diseases from animal sources include extensive exposure and rapid virus evolution (8), which facilitate human-to-human transmission. The growth of the demand for wildlife in markets in Guangdong in the past 15 years has provided an ideal platform to facilitate interspecies virus transmission from animals to humans. Such factors could even directly trigger a zoonotic disease outbreak. Our observations distinguished two distinct serologic patterns. The high ratio of antibodies to the animal virus compared to the relatively low ratio of antibodies to the human virus in a small proportion of healthy adults >2 years ago signifies the circulation of a SARS-CoV–like virus and its ineffective propagation in the human population. Following rapid virus evolution and in the presence of an unknown trigger, the novel SARS-CoV may have effectively adapted to the human host, as illustrated by a second pattern characterized by a higher human-to-animal virus antibody titer in infected persons. Although this pilot study was limited by an unstandardized design of sample collection, our preliminary findings suggest that the occurrence of SARS might not be due to an isolated cross-species transmission event, but rather to the rapid evolution of a related virus that has taken root in the human population. This implies an expected pattern of potential SARS recurrence. Measuring the prevalence of the two antibodies in different species of animals and persons who had close contact with the animals is important to improve our understanding of SARS-CoV transmission dynamics.

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Susceptibility of Pigs and Chickens to SARS Coronavirus

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An outbreak of severe acute respiratory syndrome (SARS) in humans, associated with a new coronavirus, was reported in Southeast Asia, Europe, and North America in early 2003. To address speculations that the virus originated in domesticated animals, or that domestic species were susceptible to the virus, we inoculated 6-week-old pigs and chickens intravenously, intranasally, ocularly, and orally with 106 PFU of SARS-associated coronavirus (SARS-CoV). Clinical signs did not develop in any animal, nor were gross pathologic changes evident on postmortem examinations. Attempts at virus isolation were unsuccessful; however, viral RNA was detected by reverse transcriptase-polymerase chain reaction in blood of both species during the first week after inoculation, and in chicken organs at 2 weeks after inoculation. Virus-neutralizing antibodies developed in the pigs. Our results indicate that these animals do not play a role as amplifying hosts for SARS-CoV.

An outbreak of severe acute respiratory syndrome (SARS) in humans, associated with a new coronavirus (SARS-CoV), has been reported in Southeast Asia, Europe, and North America (1–3). According to the World Health Organization, SARS affected more than 8,200 people worldwide and killed more than 700. The sequence analysis of SARS-CoV suggests that it is substantially distinct from all other known coronaviruses (1,2). Based on the nucleotide sequence, the virus is speculated to have evolved and been maintained in an animal host. However, no conclusive data have been presented to date on a possible reservoir for this virus. Our study aimed to address the role of domestic animals in the outbreak, both from the public health perspective (as a potential source of virus for human infections) and the animal health perspective. A potential susceptibility of domestic species to SARS-CoV would have major implications on the management of livestock operations worldwide.

We have experimentally inoculated chickens and swine. Both species are natural hosts for a number of viruses from the same family as SARS-CoV (*Coronaviridae*). The infectious bronchitis virus of chickens, although distinct, groups genetically most closely with SARS-CoV (1,2). Swine can host several coronaviruses (hemagglutinating encephalomyelitis virus, transmissible gastroenteritis virus [TGEV], and porcine respiratory coronavirus [PRCV]). In addition, continuous cultures of porcine turbinate cells (PT-K75) and primary chicken embryo epithelial kidney cells supported SARS-CoV replication.

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Material and Methods

Animals

Six 4-week-old crossbred pigs were kept for 2 weeks to acclimatize before being inoculated. The pigs, obtained from a high health status herd (Sunnyside Colony LTD, Sunnyside, Manitoba), had preexisting antibodies against PRCV, likely of maternal origin (4), which decreased during the experiment, as determined by competitive enzyme-linked immunosorbent assay performed by the Veterinary Services Branch of Manitoba Agriculture and Food.

Six-week-old, nonvaccinated, specific-pathogen-free chickens (White Leghorn), obtained from ADRI Nepean (Nepean, Ontario) were kept for 3 days to acclimatize before inoculation. They were housed in chicken isolators inside a biosafety level 4 (BSL4) animal cubicle. Animal housing and all animal manipulations were approved by the Animal Care Committee of the Canadian Science Centre for Human and Animal Health and met the Canadian Council on Animal Care guidelines.

Virus

SARS-CoV was plaque purified from a human isolate (Tor 3) on Vero E6 cells by using the plaquing method we describe in the SARS-CoV antibody detection section. Virus stock for animal inoculation was prepared and titrated on Vero V76 cells. Virus replication in Vero E6, Vero V76, and PT-K75 cells was compared by employing the following plaque assay: an aliquot of each virus dilution was added in duplicate onto cell monolayers in 12-well

plates (Costar, Corning, NY). Virus inoculum was then incubated on cells for 1 h at 37°C, 5% CO_2, and removed. The cells were overlayed with 2% carboxymethyl-cellulose (Sigma, St. Louis, MO)/ Dulbecco modified Eagle medium (DMEM) (Wisent, St. Bruno, Quebec), and incubated at 37°C, 5% CO_2, for 4 days. At the end of the incubation, the cells were fixed with 4% formaldehyde and stained with crystal violet. The experiment was repeated twice.

Cells

Vero E6 and Vero V76 (ATCC) cells were maintained in 10% fetal bovine serum (FBS)/DMEM medium (Sigma). Porcine turbinate PT-K75 (ATCC) cells were maintained in 10% FBS/ DMEM (Wisent). Quail QT-35 (ATCC) cells were maintained in 10% FBS/MEM-alpha medium (Mediatech Cellgro, Herndon, VA).

For the preparation of primary chicken embryo kidney epithelial cells (CEKEC), kidneys were harvested from 18-day-old chicken embryos and digested with 3 U of pronase (Sigma)/mL in citrate buffer (1.5 mM KCl, 27 mM sodium citrate, 8 mM KH_2PO_4, 5.6 mM Na_2HPO_4, pH 7.3) by repeated incubation for 2 min at 37°C with stirring. Cells were collected into fetal bovine serum and washed extensively with phosphate-buffered saline before being seeded into 24-well plates (Costar). Cells were seeded at a density of 10^6 cells/cm^2 in 1% FBS/Williams medium (Sigma) for the virus isolation. The cell suspension contained about 95% epithelial cells and 5% fibroblasts after 24 h of incubation, as previously determined by immunofluorescent assay; markers for epithelial cells (cytokeratin) and fibroblasts (vimentin) were detected.

Experimental Infection

The preimmune serum from chickens and pigs was collected 2 days before inoculation. Six-week-old pigs were inoculated simultaneously by four routes, intravenously, intranasally, ocularly, and orally, with 2 x 10^6 PFU of SARS-CoV per pig. Six-week-old chickens were inoculated by the same routes with 10^6 PFU of SARS-CoV per chicken. Three pigs and three chickens were mock inoculated and served as negative controls. Both species were divided into two groups, and blood, nasal (nares), throat, and rectal (cloacal) swabs were collected on alternate days, starting at 2 days after inoculation (dpi) and ending at 7 dpi. On days 6, 7, 13, 14, 15, and 16 after inoculation, one pig and one chicken per day were euthanized. In addition to swabs and blood, samples from lung, trachea, liver, heart, spleen, kidney, tonsil (pig), and jejunum were collected at postmortem examination. All experimental work was carried out in BSL4 containment.

Virus Isolation

Virus isolation from porcine samples was attempted on Vero V76 and porcine turbinate cells PT-K75, seeded at a density of 2 x 10^5 cells/cm^2 in 12-well plates (Costar) 24 h before inoculation. Samples were tested in duplicate twice, by plaque assay (described in Virus section) and monitoring cytopathic effect (CPE), followed by reverse transcriptase–polymerase chain reaction (RT-PCR) to detect virus replication. In addition, virus isolation from chicken samples was attempted on chicken embryo epithelial kidney cells, seeded at a density of 10^6 cells/cm^2 in 24-well plates (Costar), using CPE format followed by RT-PCR.

The tissues were ground in a MiniMix blender (Topac, Hingham, MA) to prepare a 10% w/v suspension in Dulbecco's PBS (Sigma) supplemented with antimicrobial drugs and stood for 1 h in the antimicrobial mix (streptomycin/vancomycin/nystatin/gentamycin). The suspension was centrifuged at 2000 x *g*, 4°C, 20 min. The supernatant was diluted 10-fold in the corresponding media for the individual cell types, and 400 μL (in duplicates) was incubated on cells for 1 h at 37°C, 5% CO_2. The inoculum was then removed and replaced with the appropriate media, supplemented with 5% FBS (Vero and PT-K75 cells) or 1% FBS (CEEKC). Plates were incubated for 5 days at 37°C, 5% CO_2. Isolation from blood and swabs was performed as for tissues without the homogenization step. The sensitivity of virus isolation was determined by spiking negative control lung tissues from one chicken and one pig with virus inoculum before homogenization, titrating out the samples on Vero E6 and Vero V76 cells, and comparing the titers to the inoculum titer, using plaque assay described in the virus section.

RT-PCR

RNA was extracted from blood and tissue samples with the TriPure Extraction kit (Roche Diagnostics, Indianapolis, IN). Three sets of primers were used in a one-step RT-PCR assay employing the Qiagen OneStep RT-PCR kit (Qiagen, Mississauga, ON): 1. NML polymerase primers: forward primer CAG AGC CAT GCC TAA CATG and reverse primer AAT GTT TAC GCA GGT AAG CG were used in the RT-PCR reaction (50°C for 30 min, 95°C for 15 min, followed by 50 cycles of 94°C for 15 s, 50°C for 30 s, 72°C for 30 s with 7-min extension at 72°C). The 389-nt amplicon is located within the RNA-dependent RNA polymerase gene (ORF 1b). 2. Nucleocapsid (N) primers: forward primer ATA ATA CTG CGT CTT GGT TC and reverse primer TGG CAA TGT TGT TCC TTG AG were used under the same reaction conditions as the first set of primers, yielding a 364-base pair (bp) long amplicon. 3. BNI polymerase primers and RT-PCR conditions were developed at the Bernhard-Nocht Institute for Tropical Medicine, Hamburg, Germany, by

C. Drosten, and published on their Web site on March 26, 2003: BNI OUT S2: ATG AAT TAC CAA GTC AAT GGT TAC (forward); BNI OUTAS: CAT AAC CAG TCG GTA CAG CTA C (reverse). The RT-PCR conditions were: 30 min at 50°C, 15 min at 95°C, followed by 50 cycles of 95°C for 10 s, 56°C for 10 s, 72°C for 20 s, and completed at 72°C for 7 min, yielding an amplicon of 195 bp.

The Qiagen OneStep RT-PCR kit was also used for the two-step RT-PCR with the following modifications: the template was incubated at 50°C for 30 min only with forward N primer followed by the incubation at 95°C for 15 min to inactivate the reverse transcriptase. Residual single-strand RNA template was removed by digestion at 37°C for 20 min with 2 U of Rnase H (Invitrogen, Burlington, ON). After both forward and reverse N primers and the Platinum Pfx DNA polymerase (Invitrogen) were added, the DNA synthesis was completed by using the above conditions for the N primers in a one-step RT-PCR. Randomly selected amplicons were sequenced with the respective primers to verify the identity of the bands. Sensitivity of the individual primer sets used in the RT-PCR assays was tested by spiking negative control lung tissues from chicken and pig with virus inoculum before homogenization, titrating out the homogenate, and running the RT-PCRs in parallel on the same RNA extracts.

SARS-CoV Antibody Detection

Porcine serum collected before inoculation and during the final bleed was tested for antibodies against SARS by a standard plaque reduction neutralizing test, as previously described (5). Briefly, mixtures of pre-titered (100 PFUs) SARS-CoV and serial twofold dilutions of animal sera were incubated at 37°C for 1 h and added to 6-well plates containing Vero E6 cell monolayers. After a 37°C incubation for 1 h, a nutrient-agar overlay was added, and the plates were placed in a CO_2 incubator for approximately 3 days. A second overlay, which contained neutral red as a vital stain, was then added. Plates were then checked periodically over the next few days for plaque formation. The highest serum dilution, which produced a plaque reduction of at least 90%, was defined as the titration end point.

Porcine Serum Cross-Reactivity with TGEV/PRCV

Serum samples collected on the pre-inoculation bleed and terminal bleed were tested for neutralizing antibodies against SARS and TGEV/PRCV by using microtiter CPE blocking assay. Each of the above viruses was diluted to 100 50% tissue culture infective dose ($TCID_{50}$)/well, mixed with doubling serial dilutions of test serum beginning at 1:5 (giving the first serum dilution 1:10), and incubated for 1 h at 37°C. The virus-serum mixtures were then added to 96-well microtiter plates (Costar) containing overnight confluent monolayers of Vero V76 cells or PT-K75 cells, for the SARS or TGEV CPE-blocking assay, respectively. The results were read after 3 days of incubation at 37°C, 5% CO_2.

Results

Preliminary tests to establish a sensitive cell system for virus replication were performed before animal inoculation and virus isolation. SARS-CoV replicated in Vero E6, Vero V76, and PT-K75 approximately to the same titer. QT-35 did not replicate SARS-CoV. Although CEKEC did not show any CPE, the virus replicated in those cells up to the approximate titer of 10^6, based on positive RT-PCR results on lysed cells and cell culture supernatant harvested 54 h after inoculation.

Animal Inoculation

Neither clinical disease nor gross pathologic changes were observed in chickens or pigs. Repeated attempts to isolate SARS-CoV from swabs, blood, and organs on Vero V76 had negative results. No significant (drop in titer within 1 log) impact of tissue processing on the infectivity of virus during virus isolation was observed by using lung tissues from one control chicken and one pig under control conditions. The tissue was spiked with SARS-CoV before homogenization, and virus recovery was compared to the correspondingly diluted inoculum on Vero E6 and Vero V76 cells (Table 1). Additional attempts at virus isolation were carried out on PT-K75 cells and, with chicken samples, on chicken embryo kidney epithelial cells. The results were again negative, as confirmed by RT-PCR on the inoculated cells.

RT-PCR assays were undertaken by using three sets of primers, one developed at the National Microbiology

Table 1. Relative sensitivity of virus isolation and RT-PCR in tissue samples spiked with the SARS virus before homogenization[a,b]

	Virus isolation (PFU/100 μL)		RT-PCR (100 μL)		
Tissue samples	Vero E6	Vero V76	NML primers	N primers	BNI primers
Virus control	-5.8	-6	-8	-10	-10
Chicken lung	-5.6	-5.75	-7	-9	-9
Pig lung	-5.5	-5.7	-7	-9	-9

[a]RT-PCR, reverse transcriptase–polymerase chain reaction; SARS, severe acute respiratory syndrome; N, nucleocapsid.
[b]The highest dilution in which the virus or the RNA were detected is given in $\log_{10}$

Laboratory during the investigation of the Toronto outbreak of SARS, which targeted the polymerase gene, a second (BNI) set also within the polymerase gene, and the third set targeting the nucleocapsid gene region. Due to the presence of 3′-coterminal nested mRNAs and genomic RNA (6,7) during coronavirus replication, nucleocapsid RT-PCR was expected to be more sensitive in samples containing replicating virus. The originally used NML primers were less sensitive than the other two sets of primers (BNI pol and N), and the samples were retested with these two sets of primers. Sensitivity of the RT-PCR employing the individual primer sets is illustrated in Table 1, as determined by using negative control lung tissues spiked with SARS-CoV. RT-PCR with the N and the BNI primers detected viral RNA equivalent to approximately $10^{-3/-4}$ PFU.

RT-PCR amplicons were detected in blood samples from chickens and pigs at 2 (pig 9, chickens 114 and 115) and 3 (pigs 10, 11, 12, chickens 116, 117, 118) dpi using the NML polymerase primers. Positive results using a two-step RT-PCR assay, aimed at detecting negative strands of viral RNA, indicated that replicating virus was present in the above positive pig and chicken blood samples (Figure). By using N primers and the BNI primers, viral RNA was detected in blood of all inoculated chickens up to 7 dpi and in chicken 113 at 15 dpi (Table 2).

No viral amplicons were generated from any of the harvested organs or swabs when the NML polymerase primers were used; however, the N primers yielded amplicons from spleens of two pigs at days 7 and 13 after inoculation, and in a number of chicken organs. Lung, kidney, and trachea were positive in some birds at 13 to 16 dpi, while liver, spleen, and jejunum samples were all negative. These results were confirmed with BNI polymerase primers (Table 3). Sequence analysis of selected amplicons confirmed the SARS-CoV nucleotide sequence.

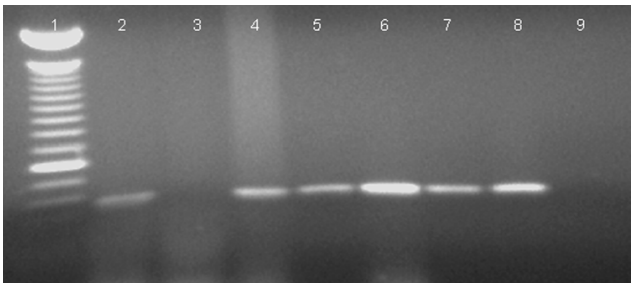

Figure. Amplification of severe acute respiratory syndrome–associated coronavirus (SARS-CoV) RNA in chicken blood, using one-step and two-step reverse transcriptase–polymerase chain reaction (RT-PCR) with nucleocapsid primers. Lane 1: 100-bp ladder, the bright band representing 600 bp; Lane 2: chicken 115, 2 days postinocuation (dpi), one-step RT-PCR; lane 3: chicken 115, 2 dpi, two-step RT-PCR (detecting negative-strand RNA); lane 4: chicken 117, 3 dpi, one-step RT-PCR; lane 5: chicken 117, 3 dpi, two-step RT-PCR; lane 6: chicken 115, 4 dpi, one-step RT-PCR; lane 7: chicken 115, 4 dpi, two-step RT-PCR; lane 8: SARS-CoV–infected cells; lane 9: negative control.

Table 2. RT-PCR on blood samples from chickens using different primer sets[a]

		Primers		
dpi	Chicken no.	NML pol	N	BNI pol
2	113	-	+	+
	114	+	+	+
	115	+	+	+
3	116	+	+	+
	117	+	+	+
	118	+	+	+
4	113	-	+	+
	114	-	-	+
	115	-	+	+
5	116	-	+	+
	117	-	+	+
	118	-	-	-
6	113	-	+	+
	114	-	+	+
	115	-	+	+
7	116	-	+	+
	117	-	-	-
	118	-	-	-
13	114	-	-	-
14	116	-	-	-
15	113	-	+	+
16	117	-	-	-

[a]RT-PCR, reverse transcriptase–polymerase chain reaction; dpi, days postinfection; pol, polymerase; N, nucleocapsid.

No SARS-CoV–neutralizing antibodies (90% reduction of virus plaques on Vero E6 cells) were detected in prebleedings from pigs and chickens. The preexisting antibodies against PRCV/TGEV in pigs did not neutralize SARS-CoV and decreased during the experiment. Neutralizing antibody against SARS-CoV developed in pigs, with titers ranging from 1:10 to 1:160 at the time of euthanasia. The SARS antibody titers corresponded for both types of virus neutralization tests (the macrotiter plaque reduction assay and the microtiter CPE blocking assay). Table 4 summarizes the changes in SARS- and TGEV-neutralizing antibodies in pigs during the course of the experiment. No antibodies >1:10 were detected in chicken serum samples on the final bleed.

Discussion

After the experimental exposure of chickens and pigs to SARS-CoV, we detected coronavirus RNA in blood and several tissues from both species starting at 2 days after inoculation. Clearance of low or nonreplicating intravenous inoculum from blood, including the viral RNA, occurs rapidly in a number of viruses (8,9). In light of the typical clearance rates and the estimated initial virus load

Table 3. Summary of RT-PCR results on chicken tissues[a]

		Lung		Trachea		Heart		Liver		Spleen		Kidney		Jejunum	
Chicken no.	dpi	N	BNI	N	BNI	N	BNI	N	BNI	N	BNI	N	BNI	N	BNI
115	6	-	-	-	-	-	-	-	-	-	-	-	-	-	-
118	7	-	-	-	-	-	-	-	-	-	-	-	-	-	-
114	13	+	+	+	+	-	-	-	-	-	-	+	-	-	-
116	14	-	-	-	-	-	-	-	-	-	-	-	-	-	-
113	15	-	-	-	-	-	-	-	-	-	-	-	-	-	-
117	16	+	-	+	-	-	-	-	-	-	-	+	+	-	-

[a]RT-PCR, reverse transcriptase–polymerase chain reaction; dpi, days postinfection; N, nucleocapsid.

Table 4. Overview of virus neutralization titers for pig preimmune and immune sera against SARS-CoV and TGEV[a]

	Pre-inoculation bleed serum antibody titer			Final bleed serum antibody titer		
Pig no.	VNT TGEV	VNT SARS	PRNT SARS	VNT TGEV	VNT SARS	PRNT SARS
7	0	0	0	0	20	10
8	20+	0	0	20	320	160
9	10	0	0	0	160	80
10	20	0	0	10	80+	80
11	10	0	0	0	40	40
12	20	0	0	0	80	80

[a]Determined by microtiter virus neutralization test (VNT) and plaque reduction neutralization test (PRNT). SARS-CoV, severe acute respiratory syndrome-coronavirus; TGEV, transmissible gastroenteritis virus.

of 5 PFU/100 µL (porcine blood), the detection of RNA, corresponding to a minimum of 10^{-3} PFU/ 100 µL, in blood at 48 h after inoculation is likely not due to a nonreplicating residual virus inoculum. Our data suggest that pigs and chickens of the age used in the experiment were infected with SARS-CoV and, to a very limited degree, supported virus replication. The unsuccessful attempts at virus isolation could be explained by a very low rate of virus replication perhaps combined with loss of infectivity during the sample collection and processing. Although the observed decrease in virus recovery (virus spiked control samples) is not significant, it may have played a role in case of the low virus load. The intravenous route likely does not represent the route of infection in a field situation, and the question of possible natural infection of chickens and pigs with SARS-CoV remains open.

Neutralizing antibodies against SARS-CoV developed in the pigs within 2 weeks of inoculation. These antibodies did not cross-react with TGEV/PRCV in a TGEV neutralization assay (PRCV and TGEV are indistinguishable in the virus neutralization assays) (10). Likewise, the preinoculation serum samples with the highest TGEV-neutralizing antibodies did not neutralize SARS-CoV, and the neutralizing antibodies against TGEV decreased as the SARS antibody titers increased. Based on the serum neutralization tests, TGEV/PRCV and SARS-CoV do not appear to be antigenically closely related, an observation supported by the initial genomic analysis (1,2). The cross-neutralization with TGEV/PRCV was initially a concern after the publication of immunohistochemical assays on SARS-CoV–infected cells (11). Since virus-neutralizing antibodies often take approximately 3 weeks to develop in chickens, no conclusions were made with regard to the low or absent antibody titers in their sera at 2 weeks after inoculation. In conclusion, the limited extent of virus replication as indicated by RT-PCR, the failure to isolate the virus, and the lack of virus shedding indicate that neither pigs nor chickens are likely to play a role as an amplifying host.

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SARS Surveillance during Emergency Public Health Response, United States, March–July 2003

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In response to the emergence of severe acute respiratory syndrome (SARS), the United States established national surveillance using a sensitive case definition incorporating clinical, epidemiologic, and laboratory criteria. Of 1,460 unexplained respiratory illnesses reported by state and local health departments to the Centers for Disease Control and Prevention from March 17 to July 30, 2003, a total of 398 (27%) met clinical and epidemiologic SARS case criteria. Of these, 72 (18%) were probable cases with radiographic evidence of pneumonia. Eight (2%) were laboratory-confirmed SARS-coronavirus (SARS-CoV) infections, 206 (52%) were SARS-CoV negative, and 184 (46%) had undetermined SARS-CoV status because of missing convalescent-phase serum specimens. Thirty-one percent (124/398) of case-patients were hospitalized; none died. Travel was the most common epidemiologic link (329/398, 83%), and mainland China was the affected area most commonly visited. One case of possible household transmission was reported, and no laboratory-confirmed infections occurred among healthcare workers. Successes and limitations of this emergency surveillance can guide preparations for future outbreaks of SARS or respiratory diseases of unknown etiology.

The emergence of severe acute respiratory syndrome (SARS) presented a challenge to public health and healthcare delivery systems worldwide. The previously unknown respiratory syndrome was characterized by nonspecific clinical symptoms, was highly transmissible in some circumstances, did not respond to antimicrobial therapy, and could rapidly progress to severe respiratory distress and death. SARS appears to have originated in Guangdong Province, China; however, the global importance of this illness was not recognized initially by local health authorities. When the World Health Organization (WHO) issued a historic global alert about cases of severe atypical pneumonia on March 12, 2003, the outbreak had spread through international travel from Guangdong Province to at least Hong Kong and Hanoi, Vietnam. There was an urgent global need for diagnosis of the etiologic agent, detection and containment of probable cases, guidance on the healthcare management of patients and potentially exposed persons, identification of measures to prevent and control infections, and timely public health communications to a wide range of audiences.

On March 14, 2003, the U.S. Centers for Disease Control and Prevention (CDC) launched an emergency public health response and established national surveillance for SARS to identify case-patients in the United States and determine if domestic transmission was occurring. We describe the surveillance system established to detect SARS in the United States, focusing on its design, challenges, and modifications that occurred as the outbreak evolved, and characteristics of the case-patients identified. Such information is critical for preparing for possible future outbreaks of SARS or other emerging microbial threats with nonspecific respiratory symptoms.

Methods

SARS Case Definition

CDC's initial surveillance definition for a suspect case of SARS (Table 1) was based on a definition first published

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Table 1. Initial SARS case definition, U.S. surveillance, March 17, 2003

Clinical criteria
Respiratory illness of unknown etiology with onset since February 1, 2003, including:
Measured temperature >38°C
Findings of respiratory illness[b]
Epidemiologic link criteria
Travel within 10 days of symptom onset to area with documented or suspected community transmission of SARS[c]
OR
Close contact[d] within 10 days of symptom onset with either a person with respiratory illness who had traveled to SARS area or a person suspected to have SARS

[a]SARS, severe acute respiratory syndrome.
[b]For example, cough, shortness of breath, difficulty breathing, hypoxia, or radiographic findings of either pneumonia or acute respiratory distress syndrome; suspect cases with either radiographic evidence of pneumonia or respiratory distress syndrome or evidence of unexplained respiratory distress syndrome by autopsy are designated "probable" cases by the WHO case definition.
[c]Hong Kong Special Administrative Region and Guangdong Province, Peoples' Republic of China; Hanoi, Vietnam; and Singapore.
[d]Having cared for, having lived with, or having had direct contact with respiratory secretions or body fluids of patient suspected to have SARS.

by WHO (1). These definitions specified clinical criteria and required a potential exposure to SARS (epidemiologic link). WHO categorized all cases with x-ray or autopsy evidence of pneumonia or respiratory distress as probable, and all others meeting the case definition were classified as suspect cases. CDC initially categorized all cases as suspect, but on April 29, 2003, CDC adopted WHO's suspect and probable classifications (2).

SARS-affected areas that constituted an epidemiologic link changed throughout the outbreak, requiring continual modification of the case definition. CDC considered an area SARS-affected if evidence of documented or suspected community transmission existed. Regions were removed from the list of SARS-affected areas when CDC-issued travel alerts or advisories were discontinued, which meant that the area had reported no new cases of SARS for 30 days.

On April 29, 2003, after a new coronavirus (SARS-CoV) was identified as the etiologic agent of SARS (3–6), the case definition was changed to incorporate criteria for laboratory-confirmed illness (7). Laboratory criteria were refined near the end of the outbreak, resulting in the final case definition on July 18, 2003 (Tables 2 and 3); revision of the requirements for a convalescent-phase serum specimen from 21 to 28 days after illness onset was not applied retrospectively, consistent with the instructions accompanying release of this case definition. This definition also introduced an exclusion criterion for suspect or probable case-patients confirmed negative for SARS-CoV infection. In this analysis, we did not apply this exclusion criterion to allow for a complete presentation of suspect and probable cases captured and monitored by national surveillance.

Table 2. CDC SARS case definition, United States, as of July 31, 2003[a]

Case classification[b]
Probable case: meets the clinical criteria for severe respiratory illness of unknown etiology and epidemiologic criteria; laboratory criteria confirmed or undetermined
Suspect case: meets the clinical criteria for moderate respiratory illness of unknown etiology and epidemiologic criteria; laboratory criteria confirmed or undetermined
Clinical criteria
Asymptomatic or mild respiratory illness
Moderate respiratory illness: temperature >38°C[c] and one or more clinical findings of respiratory illness (e.g., cough, shortness of breath, difficulty breathing, hypoxia)
Severe respiratory illness: criteria for moderate respiratory illness with radiographic evidence of pneumonia, respiratory distress syndrome, or autopsy findings consistent with pneumonia or respiratory distress syndrome without an identifiable cause
Epidemiologic link criteria
Travel (including airport transit) within 10 days of onset of symptoms to area with current or recently documented or suspected community transmission of SARS (Table 3) or close contact[d] within 10 days of symptom onset with person known or suspected to have SARS
Laboratory criteria[e]
Confirmed: detection of antibody to SARS-CoV in a serum sample; detection of SARS-CoV RNA by RT-PCR confirmed by a second PCR assay by using a second aliquot of the specimen and a different set of PCR primers; or isolation of SARS-CoV
Negative: absence of antibody to SARS-CoV in convalescent serum obtained >28 days after symptom onset[f]
Undetermined: laboratory testing not performed or incomplete
Exclusion criteria
Illness fully explained by alternative diagnosis[g]
Convalescent-phase serum sample (obtained >28 days after symptom onset) negative for antibody to SARS-CoV.
Case reported on basis of contact with index case subsequently excluded as SARS, provided other epidemiologic exposure criteria are not present

[a]CDC, Centers for Disease Control and Prevention; SARS, severe acute respiratory syndrome; CoV, coronavirus; RT-PCR, reverse transcriptase–polymerase chain reaction.
[b]Asymptomatic SARS-CoV infection or clinical manifestations other than respiratory illness might be identified as more is learned about SARS-CoV infection.
[c]Measured documented temperature of >38°C is preferred; however, clinical judgment should be used when evaluating patients for whom temperature of >38°C has not been documented. Factors that might be considered include patient self-report of fever, use of antipyretics, presence of immunocompromising conditions or therapies, lack of access to health care, or inability to obtain a measured temperature. Reporting authorities should consider these factors when classifying patients who do not strictly meet the clinical criteria for this case definition.
[d]Close contact is defined as having cared for or lived with a person known to have SARS or having a high likelihood of direct contact with respiratory secretions or body fluids of a patient with SARS. Examples of close contact include kissing or embracing, sharing eating or drinking utensils, close conversation (<3 feet), physical examination, and any other direct physical contact. Close contact does not include activities such as walking near a person or sitting across a waiting room or office for a brief period.
[e]Assays to diagnose SARS-CoV infection include enzyme-linked immunosorbent assay, indirect fluorescent-antibody assay, and RT-PCR assays of appropriately collected clinical specimens. Absence of SARS-CoV antibody from serum obtained <28 days after illness onset,[f] a negative PCR test, or a negative viral culture does not exclude SARS-CoV infection and is not considered a definitive laboratory result. In these instances, a convalescent-phase serum sample obtained >28 days after illness is needed to determine infection with SARS-CoV.[f] All SARS diagnostic assays are under evaluation.
[f]Does not apply to serum samples collected before July 11, 2003. Testing results from serum samples collected before July 11, 2003 and between 22 and 28 days after symptom onset are acceptable and will not require collection of additional sample >28 days after symptom onset.
[g]Factors that may be considered in assigning alternate diagnoses include strength of epidemiologic exposure criteria for SARS, specificity of diagnostic test, and compatibility of clinical presentation and course of illness for alternative diagnosis.

Table 3. Travel criteria for persons with suspect or probable SARS, United States[a]

Area	First date of illness onset for inclusion as reported case[b]	Last date of illness onset for inclusion as reported case[c]
China (Mainland)	November 1, 2002	July 13, 2003
Hong Kong	February 1, 2003	July 11, 2003
Hanoi, Vietnam	February 1, 2003	May 25, 2003
Singapore	February 1, 2003	June 14, 2003
Toronto, Canada	April 1, 2003	July 18, 2003
Taiwan	May 1, 2003	July 25, 2003
Beijing, China	November 1, 2002	July 21, 2003

[a]SARS, severe acute respiratory syndrome.
[b]The World Health Organization has specified that the surveillance period for China should begin on November 1; the first recognized cases in Hong Kong, Singapore, and Hanoi (Vietnam) had onset in February 2003. The date for Toronto is linked to laboratory-confirmed case of SARS in a U.S. resident who had traveled to Toronto; the date for Taiwan is linked to the Centers for Disease Control and Prevention (CDC) travel recommendations.
[c]The last date for illness onset is 10 days (i.e., one incubation period) after removal of a CDC travel alert. The case-patient's travel should have occurred on or before the last date the travel alert was in place.

Inclusion Criteria

Case-patients were eligible for inclusion if they were U.S. residents and were present in the United States during some of their illness. Non-U.S. residents who became ill or in whom SARS was diagnosed while they were in the United States were monitored as patients of special interest until April 30, 2003, after which they were included in surveillance. U.S. citizens who were not present in the United States for any period of their illness were not included in surveillance.

National Surveillance for SARS

National surveillance began on March 17, 2003, 3 days after CDC initiated its emergency response. The analysis in this report covers the period March 17 through July 30, 2003, 3 weeks after WHO declared the global outbreak over. Case definitions were distributed to state and local health departments through CDC's Epidemic Information Exchange (Epi-X), a secure communications network for public health professionals, and through CDC's Health Alert Network. Case definitions were also posted on a CDC Web site dedicated to SARS. A case report form was developed to collect demographic and clinical data as well as information about epidemiologic links. This form was also distributed through Epi-X and by electronic mailings by the Council of State and Territorial Epidemiologists (CSTE) to its membership. The case report form was modified as the outbreak evolved.

At the beginning of the outbreak, health departments were requested to report to CDC all respiratory illnesses that they thought should be evaluated for SARS. Although the communication chain for reporting these illnesses to health departments varied by state, all health departments relied on passive reporting from clinicians rather than actively seeking to identify potential cases. CDC hosted weekly teleconferences with state and local health departments to address developing issues related to the domestic surveillance and response. An Atlanta-based CDC team received illness reports by telephone or fax. State and local health department personnel collected data, completed case report forms, and determined case status in consultation with CDC. When a patient met the case definition, data about that person were added to a "line list," which was updated and analyzed daily. Hospitalized case-patients were actively monitored to establish outcomes, as were persons who had pending data that could alter case status. Illnesses that failed to meet the case definition on subsequent investigation (e.g., patient's travel history clarified) were removed from the line list. The data collection system at both the health departments and CDC was paper-based rather than electronic or online. Epidemiologic data were entered at CDC into an electronic database that was merged with laboratory data.

Laboratory Confirmation of SARS Infection

State and local health departments were asked to collect acute- and convalescent-phase serum and stool specimens and nasopharyngeal or oropharyngeal swab samples from all case-patients. Before the cause of SARS was established, specimens were tested for a wide array of bacterial and viral pathogens at CDC. After SARS-CoV was discovered, serum specimens were tested for SARS-CoV antibodies, and respiratory and stool specimens were tested for SARS-CoV by polymerase chain reaction (PCR) (4). Diagnostic testing was initially centralized at CDC. Later, reagents for SARS-CoV antibody and nucleic acid testing were made available to state public health laboratories and the Laboratory Response Network (8). To meet U.S. Food and Drug Administration requirements for the use of nonlicensed tests in these laboratories, CDC developed informed-consent documents and informational materials that clinicians used when collecting specimens for SARS-CoV testing from their patients. Case-patients were classified as confirmed, negative, or undetermined for SARS-CoV infection (Tables 2 and 3). On July 18, 2003, the 21-day period required for convalescent-phase specimens was extended to 28 days for newly identified cases on the basis of evidence that seroconversion sometimes occurred after day 21 (9).

Laboratory Testing for Other Respiratory Pathogens

During the course of the outbreak, testing for alternative causes that could fully explain patient illness was ordered at the discretion of local clinicians, and SARS was often excluded on the basis of local interpretations of test results. Many of these illnesses were never reported to CDC. Diagnostic testing for alternative agents was performed at CDC early in the outbreak. In addition, evaluation of acute

respiratory specimens and paired serum specimens from suspect and probable case-patients for evidence of the following respiratory pathogens was completed after the outbreak was over: *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, *Chlamydia pneumoniae*, *C. psittaci*, *Legionella pneumophila*, influenza viruses types A and B, respiratory syncytial virus, parainfluenza viruses types 1, 2, and 3, human metapneumovirus (HMPV), and adenovirus. *M. pneumoniae* immunoglobulin (Ig) G and IgM antibodies were measured by using the REMEL *Mycoplasma pneumoniae* IgG/IgM Antibody Test System (REMEL Inc., Lenexa, KS). *S. pneumoniae* IgG antibodies to pneumococcal surface adhesin A protein (PsaA) were measured by using a PsaA-ELISA (enzyme-linked immunosorbent assay) as previously described (10). A rise in IgG antibody titers of twofold or more between acute- and convalescent-phase serum pairs was considered positive for a pneumococcal exposure or event. *Chlamydia* IgG and IgM antibodies were measured by using a microimmunofluorescent antibody assay (Focus Technologies, Cypress, CA). *L. pneumophila* antibodies were measured by using an indirect immunofluorescent antibody assay (11). Specific IgG antibodies to the respiratory viruses (excluding influenza) were measured by using an indirect enzyme immunoassay panel, following procedures previously described for HMPV (12). A rise in IgG antibody titers of fourfold or greater between acute- and convalescent-phase serum pairs was considered positive for recent virus infection. Serologic analysis for influenza was performed by hemagglutination-inhibition assay. All serum specimens were treated with receptor-destroying enzyme to remove nonspecific inhibitors before testing (13).

Specimens from some or all of the following sources were tested by PCR for evidence of bacterial or viral infection: bronchoalveolar fluid, sputum, tracheal aspirates, nasal washings, and nasal, nasopharyngeal, and oropharyngeal swab samples. All the bacterial methods used have been described previously (11,14–16) except the *L. pneumophila* real-time PCR assay (Online Appendix).

Total nucleic acid was extracted from 100 µL of specimen by using the QIAamp Virus BioRobot MDx kit (QIAGEN Inc., Valencia, CA). Reverse transcriptase (RT)–PCR assays for influenza A and B viruses; respiratory syncytial virus; human parainfluenza viruses 1, 2, and 3 (17); and HMPV (12) were performed as previously described. RT-PCR assays for adenovirus and picornavirus (inclusive of rhinovirus and enterovirus) were performed by using these same amplification conditions with primer pairs to the conserved regions of the hexon gene and the 5′-untranslated region: adenovirus [(+) 5′-CCC(AC)TT(CT)AACCAC-CACCG-3′; (-) 5′-ACATCCTT(GCT)C(GT) GAAGTTC-CA-3′] and picornavirus [(+) 5′-GGCCCCTGAATG (CT)GGCTAA-3′; (-) 5′-GAAACACGGACACCCAAA GTA-3′]. All nucleic acid extracts were also tested by RT-PCR for the GAPDH housekeeping gene to ensure RNA integrity and absence of RT-PCR inhibitors.

Results

From March 17 to July 30, 2003, CDC received reports of 1,460 respiratory illnesses under evaluation for SARS, of which 398 (27%) met the case definition for suspect or probable SARS before laboratory-based exclusion criteria for SARS-CoV–negative status were applied (Figure 1). Seventy-two (18%) of those meeting the case definition

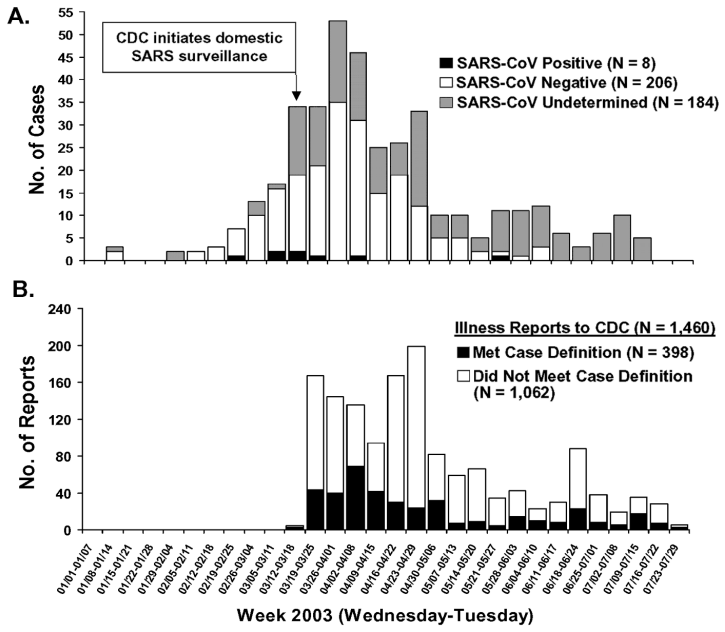

Figure 1. A) Number of U.S. severe acute respiratory syndrome (SARS) cases reported to Centers for Disease Control and Prevention (CDC) by week of illness onset (N = 398[a]) and B) number of unexplained respiratory illness reports received by CDC by week of illness report (N = 1,460), January–July 2003. (SARS-CoV, severe acute respiratory syndrome–associated coronavirus).

had chest x-ray evidence of pneumonia and were classified as probable case-patients. Eight case-patients (2%) were confirmed to be positive for SARS-CoV, 206 (52%) were confirmed to be negative for SARS-CoV by serologic testing, and 184 (46%) had undetermined SARS-CoV status because of the absence of convalescent-phase serum samples. Cases were reported from 41 states and Puerto Rico, with the highest case counts in California (74), New York (51), and Washington (30); no cases were reported from 9 states or the District of Columbia (Figure 2).

Of the eight confirmed SARS-CoV–positive case-patients, all had radiographic evidence of pneumonia and six were identified in the first month of surveillance (Table 4). Five traveled to Hong Kong, two to Toronto, and one to Singapore. Further case details have been presented elsewhere (18–21). Among the eight confirmed SARS-CoV–positive case-patients, seven had illnesses that were associated solely with travel to an affected area. Although the eighth case-patient traveled with her spouse (subsequently confirmed as a case-patient) to an affected area (Hong Kong, where both stayed in a hotel in which intense local transmission occurred [22]), the epidemiologic link was classified as close contact because the onset of illness occurred 13 days after the couple's return to the United States (18,20).

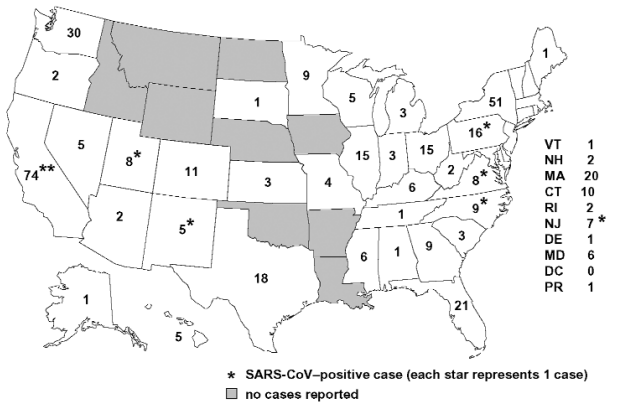

Figure 2. Number of suspect and probable cases of severe acute respiratory syndrome (SARS) cases reported to Centers for Disease Control and Prevention March 17–July 30, 2003, by state of residence (N = 398). (SARS-CoV, severe acute respiratory syndrome–associated coronavirus).

The median age of all suspect and probable case-patients was 39 years (range 3 months to 91 years), and 53% were male (Table 4). Almost one third (124/398,

Table 4. Characteristics of SARS case-patients, U.S. SARS surveillance, March 17–July 18, 2003[a]

	Overall		SARS-CoV positive	SARS-CoV negative		SARS-CoV undetermined	
Characteristic	Probable, % (n = 72)	Suspect, % (n = 326)	Probable, % (n = 8)	Probable, % (n = 39)	Suspect, % (n = 167)	Probable, % (n = 25)	Suspect, % (n = 159)
Age (years)							
0–4	15	14	0	15	10	20	19
5–9	4	4	0	3	5	8	4
10–17	3	2	0	5	2	0	0
18–64	58	73	100	54	76	52	70
≥65	20	7	0	23	7	20	7
Sex							
Female	44	47	50	41	50	48	45
Male	56	53	50	59	50	52	55
Race							
White	47	58	37	54	62	40	53
Black	1	2	0	0	2	4	1
Asian	40	33	63	36	28	40	38
Other	2	0	0	2	0	0	2
Unknown	10	7	0	8	8	16	6
Exposure							
Travel	83	81	88	87	82	84	81
Close contact	14	16	12[b]	13	17	8	14
Health care worker	0	1	0	0	0	0	1
Unknown	3	2	0	0	1	8	4
Hospitalized							
Yes	61	25	88	59	26	56	23
No	39	75	12	41	73	44	75
Unknown	0	1	0	0	1	0	2
Mechanically ventilated							
Yes	3	1	12	0	1	4	1
No	89	93	88	97	95	80	91
Unknown	8	6	0	3	4	16	8

[a]SARS-CoV, severe acute respiratory syndrome–associated coronavirus.
[b]This case-patient also traveled to Hong Kong and stayed at Hotel M; however, onset of illness was 13 days after returning to the United States.

31%) of the patients were hospitalized. The median length of hospitalization for the 90 persons with adequate hospitalization duration data was 3 days (range 1–14). Twenty-one percent of hospitalized patients (19/91 patients with data on intensive care unit admissions) were admitted to an intensive care unit; only 2 of the 8 SARS-CoV–positive case-patients were admitted to intensive care units. Among all 398 suspect and probable case-patients, 4 (1%) required mechanical ventilation, one of whom was SARS-CoV positive (Table 4). No deaths were reported.

Travel to an affected area was the most commonly reported epidemiologic link (83% of cases). Mainland China was the most frequent destination (39% of travelers), followed by Hong Kong (38%), and Toronto (18%); 22% of case-patients traveled to more than one affected area. The frequency of travel to China, Hong Kong, and Toronto among SARS case-patients is shown by date of illness onset in Figure 3; the periods during which these areas were considered SARS-affected for surveillance purposes are also shown.

No healthcare workers with suspect or probable SARS (n = 31) were confirmed to be SARS-CoV positive; 17 (55%) were confirmed SARS-CoV negative, and the remainder had undetermined SARS-CoV status. The only possible case of recognized secondary transmission was between the married couple described above.

Number of Illnesses Reported and Completeness of Surveillance Data

The number of illnesses reported was highest during the first 6 weeks of surveillance and varied over the course of the outbreak (Figure 1). Among suspect and probable cases, the completeness of critical surveillance variables related to case definition and severity of illness was as follows: date of symptom onset, 98%; radiologic chest imaging for pneumonia, 80%; hospitalization status, 99%; hospital discharge date for admitted case-patients, 73%; and healthcare worker as occupation, 94%. Although collection of convalescent-phase sera was essential for assessing infection with SARS-CoV, samples needed for definitive laboratory determination of case status were not obtained from 46% of patients (probable case-patients: 35%; suspect case-patients: 49%; chi-square = 4.68; p = 0.03).

Surveillance System Sensitivity and Predictive Value

Sensitivity refers to the proportion of SARS-CoV cases in the population that were detected by the surveillance system (23). Because SARS-CoV confirmatory laboratory testing was performed only on patients identified by the surveillance system, we cannot evaluate sensitivity for the system overall. If we limit analysis to the population of suspect and probable cases with definitive laboratory results (N = 214), we can evaluate the sensitivity of the probable case definition; all the confirmed SARS-CoV–positive patients (N = 8) had been classified as probable cases, leading to a sensitivity of 100%. The predictive value positive refers to the proportion of reported cases that actually have the health-related event under surveillance (SARS-CoV infection). The predictive value positive among cases with definitive laboratory results was 4% (8/214). The predictive value positive among the 47 probable cases with definitive laboratory results was 17%.

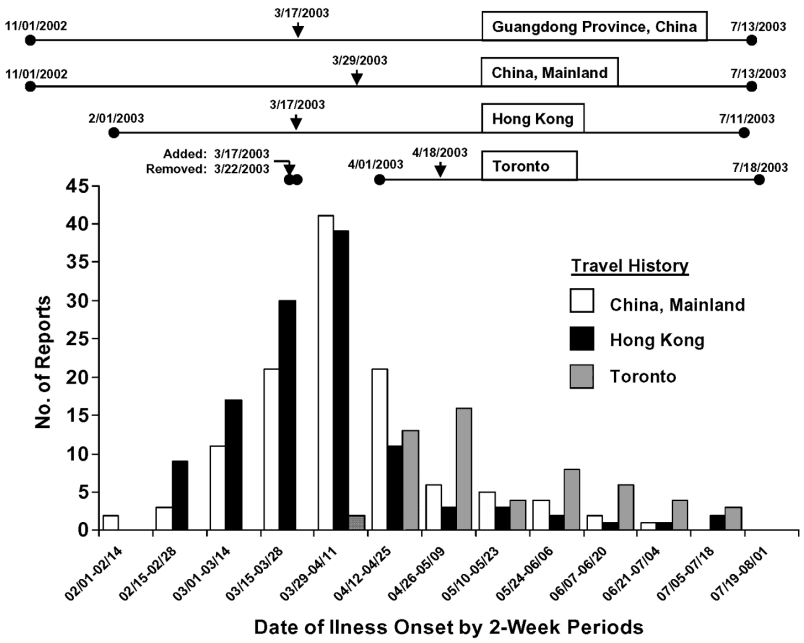

Figure 3. Number of suspect and probable cases reporting travel within the past 10 days to mainland China, Hong Kong, and Toronto, by date of illness onset (N = 307). Lines between solid circles denote periods during which onset of illness within 10 days of travel to the area fulfilled epidemiologic criteria for inclusion as a case of severe acute respiratory syndrome (SARS). Arrows denote the date on which an area was added to the U.S. surveillance case definition as SARS-affected.

Table 5. Results of diagnostic testing for other infectious respiratory pathogens, U.S. SARS surveillance, March–July, 2003

SARS-CoV status	*Mycoplasma pneumoniae*	*Streptococcus pneumoniae*	*Chlamydia pneumoniae*[d]	*Legionella pneumophila*	HMPV	Influenza A or B	Para-influenza 1, 2, or 3	RSV	Adenovirus	Picornavirus[e]
Positive										
Chest imaging results[f] positive	0/2 (0%)	0/1 (0%)	0/2 (0%)	0/2 (0%)	0/1 (0%)	1/1 (100%)	0/1 (0%)	0/1 (0%)	0/1 (0%)	--
Negative										
Chest imaging results positive	3/24 (13%)	0/16 (0%)	0/24 (0%)	0/24 (0%)	2/22 (9%)	0/21 (0%)	1/22 (5%)	0/22 (0%)	0/22 (0%)	3/10 (30%)
Chest imaging results negative	11/99 (11%)	5/71 (7%)	2/95 (2%)	0/96 (0%)	8/90 (9%)	16/84 (19%)	5/90 (6%)	2/90 (2%)	5/90 (6%)	12/45 (27%)
Undetermined										
Chest imaging results positive	3/14 (21%)	1/1 (100%)	0/15 (0%)	0/14 (0%)	1/13 (8%)	1/13 (8%)	2/13 (15%)	0/13 (0%)	1/13 (8%)	4/13 (31%)
Chest imaging results negative	5/61 (8%)	0/1 (0%)	0/61 (0%)	0/60 (0%)	1/47 (2%)	7/47 (15%)	4/47 (9%)	1/47 (2%)	3/47 (6%)	10/46 (22%)
Totals	22/200 (11%)	6/90 (7%)	2/197 (1%)	0/196 (0%)	12/172 (7%)	25/166 (15%)	12/172 (7%)	3/172 (2%)	9/172 (5%)	29/114 (25%)

[a]SARS, severe acute respiratory syndrome; CoV, coronavirus; HMPV, human metapneumovirus; RSV, respiratory syncytial virus; PCR, polymerase chain reaction.
[b]Denominators for results of tests vary as specimens of appropriate type and of adequate amount necessary for PCR and serologic testing were obtained only for a subset of case-patients. Positive results shown are those persons for whom evidence of acute infection was demonstrated by serologic and/or PCR testing on the specimens available for testing.
[c]Only one of the two SARS-CoV–positive case-patients had evidence of infection with another agent (influenza B). For 22 suspect and probable cases, more than one agent was identified. Combinations included: HMPV, Influenza B (FluB) + *S. pneumoniae* (N = 1); *Mycoplasma*, picornavirus + *S. pneumoniae* (N = 1); *Mycoplasma* + FluA (N = 5); HMPV + parainfluenza virus (HPIV) (N = 1); *C. pneumoniae*, adenovirus + FluB (N = 1); *Mycoplasma* + picornavirus (N = 3); adenovirus + picornavirus (N = 1); *Mycoplasma* + HPIV (N = 1); HPIV + picornavirus (N = 1); FluB + picornavirus (N = 1); adenovirus + HMPV (N = 1); HPIV + picornavirus (N = 1); HMPV + picornavirus (N = 1); *Mycoplasma* + picornavirus (N = 1); *S. pneumoniae* + picornavirus (N = 1); *S. pneumoniae* + HMPV (N = 1).
[d]All specimens tested for serologic or PCR evidence of *C. pnuemoniae* were also tested for evidence of *C. psittaci*; no acute *C. psittaci* infections were diagnosed.
[e]Inclusive of rhinovirus and enterovirus.
[f]Plain film x-ray, computed tomographic scan, etc.

Flexibility and Timeliness of Surveillance

The United States was one of many countries reporting SARS cases to WHO, which established international case definitions and reporting standards. Although flexibility was limited by the need to maintain harmonized international surveillance, U.S. surveillance remained flexible enough to incorporate frequent modifications rapidly. For example, when mainland China was added to the list of SARS-affected areas, within hours, case-patients who traveled to provinces other than Guangdong were added to the line list, and travel to mainland China quickly became the most common travel exposure (Figure 3).

The median time between symptom onset and reporting suspect or probable cases to CDC decreased during the first 12 weeks of national surveillance from 8 to 3 days. After week 12, the median time to national reporting increased to a median of 15 days, with 40% (30/76) of cases reported >50 days after illness onset. Data on date illness was reported to local and state health departments were not collected.

Evaluation of Alternative Respiratory Pathogens

Among the 201 suspect and probable case-patients for whom serologic or PCR testing was performed at CDC, 95 (47%) demonstrated evidence of at least one alternative respiratory infection. Among specimens tested, picornavirus (enterovirus/rhinovirus) was the most common pathogen identified (29 of 114, 25%), followed by human influenza A or B virus (25/166 [15%]) and *M. pneumoniae* (22/200, 11%; Table 5). Patients with probable and suspect cases of SARS were equally likely to have an alternate cause identified (46% each). SARS-CoV–negative case-patients and those with unknown SARS-CoV status were also equally likely to have an alternate cause identified (45% and 49%, respectively). Adequate specimens were available for only two of the eight SARS-CoV–positive case-patients, one of whom also showed a fourfold or greater rise in antibodies to influenza B.

Discussion

During the U.S. emergency public health response to SARS, >1,000 unexplained respiratory illnesses were reported by state and local health departments to CDC. Countless additional illnesses were investigated and rapidly ruled out for SARS by state and local health departments. Despite the large surveillance burden, discovery of the etiologic agent for SARS and development of effective diagnostic tests showed that the United States experienced limited SARS activity during the global outbreak, similar to much of Europe, Africa, Australia, and South America. There was no evidence of community transmission in the United States even though SARS-affected countries were common travel destinations for U.S. residents. Investigation of close contacts of the eight U.S. SARS-CoV–infected patients yielded one instance of secondary domestic transmission, although travel-related exposure cannot be definitively excluded for

this case (18,20), and the source of exposure is considered undetermined by WHO. In addition, no healthcare workers identified by national surveillance had laboratory evidence of SARS infection, despite evidence of unprotected exposures to confirmed case-patients (24). While effective surveillance and timely infection-control measures likely helped limit transmission, why the United States experienced few SARS-CoV infections despite opportunities for importation and spread remains unclear.

National surveillance during the emergency response met important surveillance objectives. It identified illness clusters for further investigation, tracked progression of the epidemic in the United States, and facilitated specimen collection from suspect and probable case-patients for SARS diagnosis. This surveillance allowed for rapid and frequent updates to the healthcare and public health communities and to the public on the status of the outbreak.

Despite these successes, the system had several important limitations. Like all passive systems, it relied on astute healthcare providers to detect and report illnesses that might have been SARS. The lack of a rapid diagnostic test that could reliably diagnose SARS-CoV infection during the early phase of illness increased the workload and anxiety of clinicians, public health personnel, patients, their contacts, and the general public. Frequent, labor-intensive contact with healthcare providers was needed to obtain updated clinical information for reported case-patients. As a result, classification of patients as suspect and probable case-patients was dynamic and often changed as new information became available. This situation sometimes created seeming discrepancies between national and state and local health department case counts, which in turn complicated public communication. The evolution of the worldwide outbreak required frequent modifications of the case definition, and establishing consistent criteria to define a SARS-affected area on the basis of community transmission was difficult. Finally, the paper-based reporting system increased the difficulty of reporting to CDC and delayed timeliness of reports, and the resulting database did not allow states immediate access to their own information.

The time between disease onset and reporting to CDC increased in the latter phase of the outbreak. This increased reporting lag may reflect the growing surveillance workload as the outbreak progressed, delays in reporting until alternative diagnoses were evaluated, or a decreasing sense of urgency fueled by low disease rates and low likelihood of confirmed SARS among U.S. case-patients and lack of evidence for community transmission. The value of remaining vigilant throughout all stages of an outbreak should not be underestimated. It was critical in the context of this outbreak that infection-control measures be rapidly implemented for all suspect and probable case-patients since a single case in any area could quickly have a global impact. Evidence from Toronto, Hong Kong, Hanoi, Singapore, and Taiwan suggests that in some circumstances a single patient led to a large number of secondary cases and chains of transmission (25,26). Moreover, although most patients with SARS show radiographic evidence of pneumonia, as was observed for all the confirmed U.S. case-patients with SARS-CoV disease, in an outbreak setting, heightened vigilance and infection-control measures should be maintained for suspect as well as probable case-patients because of growing evidence that a small proportion of patients may not exhibit evidence of pneumonia and because features of pneumonia often do not develop until days 4–7 of illness (27,28). The timeliness of infection-control measures implemented for U.S. case-patients could not be assessed because relevant data were not collected as part of national surveillance.

The clinical signs and symptoms of SARS infections are similar to that of other respiratory illnesses. Empiric management of patients with respiratory illness, limited state and local capacity to perform reliable respiratory diagnostics, and lack of national surveillance for respiratory syndromes, such as pneumonia, complicated the challenge of rapid identification of SARS patients. Comprehensive testing for a variety of respiratory pathogens among patients with suspect and probable cases found that 46% had evidence of a possible infection with bacterial and viral respiratory pathogens other than SARS-CoV. Our finding that one case-patient with confirmed SARS-CoV also tested positive for influenza B infection is consistent with accumulating evidence that co-infections involving SARS-CoV and other bacterial or viral respiratory pathogens occur (29,30). This underscores the importance of obtaining convalescent-phase serum samples to make final determinations about infection with SARS-CoV and of maintaining infection-control measures despite identification of alternative agents. Moreover, in determining alternative diagnoses, the strength of the epidemiologic exposure criteria for SARS, the specificity of the diagnostic test, and the compatibility of the clinical signs and symptoms and course of illness for the alternative diagnosis should be taken into account (Tables 2 and 3). Testing for respiratory pathogens could not be completed until after the outbreak; this precluded timely re-assessment of case-patients to determine if an agent other then SARS-CoV was most likely responsible for the clinical illness. To help facilitate more timely diagnostic evaluation, CDC plans to develop real-time PCR assays for important respiratory pathogens for use by public health laboratories. Improving local capacity for diagnosing respiratory illness should strengthen national preparedness for respiratory illness threats.

In June 2003, the Council of State and Territorial Epidemiologists (CSTE) added respiratory illness due to

SARS-CoV to the list of nationally reportable diseases. CDC has adopted the case definitions detailed in the CSTE position statement (31). This new definition, which was updated again on October 30, 2003, will improve the predictive value positive of national surveillance by considering "reports under investigation" that require monitoring and infection control as separate from cases of confirmed SARS-CoV disease that will be reported to the national system. The statement sets the stage for future SARS surveillance. CDC has developed a SARS preparedness plan for the United States that outlines in more detail recommendations for surveillance (32); as part of preparedness efforts, a Web-based surveillance module for SARS-CoV disease reporting is now in place.

In the absence of recognized SARS cases, initial surveillance will likely consist of sentinel case detection with a focus on unexplained illnesses in healthcare workers and travelers returning from areas that were affected by SARS in the recent global outbreak. Because hospitals experienced high rates of transmission in affected areas, infection-control teams may additionally institute passive or active surveillance for pneumonia or fevers among staff and patients, combined with diagnostic testing for SARS-CoV. The intensity of surveillance efforts will need to be tailored to the degree of local transmission within both the community and healthcare facilities. Contact tracing should rapidly identify possible early cases of secondary SARS and any unrecognized sources of infection for persons without epidemiologic links.

Challenges remain, including how best to allocate limited public health resources for preparedness planning in light of the world's limited experience with SARS infections and how to synchronize national case definitions and reporting requirements with the systems established by international agencies, such as WHO. Although whether SARS will become a recurring problem is unclear, lessons learned while preparing for that eventuality will be important for other global infectious disease outbreaks.

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Introduction of SARS in France, March–April, 2003

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We describe severe acute respiratory syndrome (SARS) in France. Patients meeting the World Health Organization definition of a suspected case underwent a clinical, radiologic, and biologic assessment at the closest university-affiliated infectious disease ward. Suspected cases were immediately reported to the Institut de Veille Sanitaire. Probable case-patients were isolated, their contacts quarantined at home, and were followed for 10 days after exposure. Five probable cases occurred from March through April 2003; four were confirmed as SARS coronavirus by reverse transcription–polymerase chain reaction, serologic testing, or both. The index case-patient (patient A), who had worked in the French hospital of Hanoi, Vietnam, was the most probable source of transmission for the three other confirmed cases; two had been exposed to patient A while on the Hanoi-Paris flight of March 22–23. Timely detection, isolation of probable case-patients, and quarantine of their contacts appear to have been effective in preventing the secondary spread of SARS in France.

Severe acute respiratory syndrome (SARS) was recently identified as a new clinical entity (1). SARS likely originated in the Guangdong Province of People's Republic of China (2) and subsequently spread worldwide as infected persons traveled. During the 2003 outbreak, SARS was primarily transmitted by person-to-person contact between healthcare workers or household members and ill patients (2). Community transmission also occurred in several of the most affected areas, and an explosive outbreak from a common source occurred in Amoy Garden in Hong-Kong (3). As of June 2003, a total of 8,477 probable cases and 811 deaths had been reported from 32 countries (4). A novel coronavirus has been identified as the cause of SARS (5–7). Based on current knowledge, SARS is transmitted from symptomatic patients by close direct or indirect contacts through respiratory droplet secretions (2). In specific situations, other modes of transmission, such as airborne spread, may be possible (8). The incubation period ranges from 2 to 10 days, allowing SARS to spread over long distances by infected persons who travel (8,9).

We describe how SARS was introduced in France through a single patient who returned from Vietnam on March 23 and present data that suggest transmission from this patient to other passengers may have occurred during his flight back from Hanoi to Paris.

Materials and Methods

After the World Health Organization (WHO) alert on March 12, 2003, a centralized surveillance system was set up for SARS in France (10). All persons who returned from an area affected by recent transmission, had been in contact with a probable case during the previous 10 days, and in whom fever was >38°C, with cough or difficult breathing, were advised to call the emergency service. These persons were transported to the closest university-affiliated infectious disease ward or one of the nine infectious disease wards designated as a regional reference center in the French plan of action against bioterrorism, using masks for droplet protection. After performing clinical and

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biologic evaluation and chest x-ray, the attending clinician notified the Institut de Veille Sanitaire through a unique telephone number. On the basis of the results of the initial and subsequent evaluations, each notified case was either discharged, kept as a suspect case, or classified as a probable case using the WHO SARS case definition (10,11). Probable and suspected case-patients were kept in isolation until recovery or until the diagnosis was changed, respectively. For this investigation, a probable case of SARS was defined as previously described (12).

For patients who fulfilled the definition of a probable case, respiratory secretion specimens were taken from the nose, throat, or sputum to detect for SARS–associated coronovirus (CoV) by reverse transcription–polymerase chain reaction (RT-PCR) (7) at the National Reference Center for Influenza (Northern France), Institut Pasteur, Paris. RNA extraction and RT-PCR mixes were prepared in designated rooms. RT-PCR procedures included appropriate negative and positive controls in each run: two negative controls for the extraction procedure and one water control and one positive control for each PCR run. Two RT-PCR, either both nested or one nested and one real-time, were performed for each sample. Real-time RT-PCR, using the SARS-CoV detection kit from Artus (Germany), included an internal control that detected PCR inhibitory substances. One-step nested RT-PCR targeting either the Bernhard Nocht Institute (BNI) or the Centers for Disease Control and Prevention (CDC) fragment of the polymerase gene was used (7,13). When real-time RT-PCR was performed, which targets the BNI fragment, the other RT-PCR was the nested RT-PCR targeting the CDC fragment of the polymerase gene. The real-time and nested RT-PCR, which targeted the BNI fragment reliably, detected 10 copies of RNA in the assay corresponding to 800 RNA molecules per milliliter of specimen.

Acute and convalescent serum samples were also obtained from probable cases. They were tested for immunoglobulin (Ig) G antibodies against the SARS-CoV using indirect immunofluorescence with Vero E6 cells infected by the SARS-CoV, negative control Vero E6 cells and fluorescein-labeled goat antihuman IgG. Results of serologic testing were considered positive either in case of seroconversion or a fourfold increase of observed titers, or if the serum exhibited a titer >160. The detection limit of our indirect immunofluorescence assay corresponded to the first dilution used: 1/40.

For each probable and confirmed case, information was collected on clinical symptoms, chest x-ray findings, leukocyte counts, illness onset date, demography, all possible contacts with a probable case, and exposures when traveling to affected area (contact with any hospital or place of potential transmission). Persons who did not use masks for droplet protection and had contact with a symptomatic probable or confirmed case of SARS were quarantined at home for 10 days after exposure and contacted daily by telephone. As recommended by WHO, this follow-up included the passengers who sat within two rows of a SARS case-patient on the Air France Hanoi-Paris flight of March 22 and 23, 2003 (14). The crew of the Air France flight was also followed for 10 days by the Air France medical service. During follow-up interviews with the passengers seated close to the index patient (patient A), we obtained a detailed description of his clinical condition, his movements in the aircraft, the contacts he may have had with other persons on board, and the timing of his boarding and deplaning in relation to other passengers, including the stopover in Bangkok. Passengers on a flight in which a person with a symptomatic probable case had traveled were informed publicly through the media and mail of the potential exposure and advised to call the emergency service phone number to be evaluated and admitted to the closest university-affiliated infectious disease ward if a fever of >38°C developed within 10 days of the flight.

We estimated the incidence density of SARS among passengers who sat within two rows of a case of SARS in the AF171 flight of March 22–23 by using the total number of person-hours as the denominator. Ninety-five percent confidence intervals (95% CI) were calculated by using the exact binomial method (15).

Results

As of April 30, a total of 394 suspected cases had been notified to the Institut de Veille Sanitaire and 5 (1.3%) met the definition of a probable case of SARS. Four were men, and their ages were 26 to 56 years. All had fever >38°C, four with nonproductive cough and two with dyspnea. None had diarrhea. Chest x-rays showed interstitial pneumonia in four patients (bilateral for three) and alveolar consolidation in one. Lymphocyte counts were 170 to 1,400/mm^3. Four patients were lymphopenic (<1,000/mm^3); the same four patients also had thrombocytopenia. Severe hypoxemia that required mechanical ventilation developed in one patient (the index case, patient A). Four patients had been discharged from the hospital within 8 to 21 days after onset, and one died (patient A) from intensive-care complications 95 days after admission.

RT-PCR was positive for SARS-CoV in at least three of the respiratory secretion samples taken on at least 2 different days after onset of symptoms for three of the five patients. Acute-phase and convalescent-phase serum samples were obtained for four of the probable cases, and seroconversion to SARS-CoV occurred in three samples, including samples from the patient for whom RT-PCR was negative (patient D, Figure 1). However, for patient D, the only respiratory samples available for RT-PCR were taken on day 2 after onset.

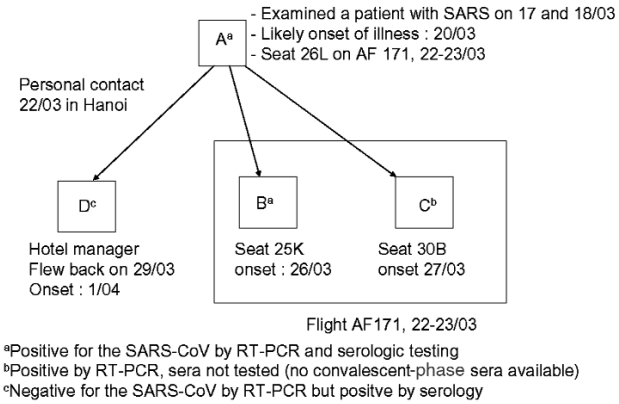

Figure 1. Cases of SARS, by date of onset and exposure, laboratory results and type of exposures, France, March-April, 2003.

Our subsequent analysis is restricted to the four confirmed cases (patient A to D, Figure 1). All four cases were related to the outbreak that occurred in the French Hospital in Hanoi, Vietnam (2). The index patient (patient A), who had worked in this hospital, was the most probable source of secondary transmission to the other three patients. On the basis of information obtained from his colleagues, on March 16 and 17, he was known to have examined, without respiratory protection from droplet secretions, an ill physician in whom SARS subsequently developed. Although no precise date of onset is available for patient A, interviews with persons he had met in Hanoi during the few days before his departure indicate that symptoms, such as cough and severe fatigue, had developed as early as March 20.

From March 26 to April 1, three secondary cases occurred (Figure 1), with incubation periods of 3, 4, and 10 days. Two cases occurred among the 371 passengers (166 boarded in Hanoi of whom 5 left in Bangkok, and 205 boarded in Bangkok) and 30 flight attendants of the Air France Hanoi-Bangkok-Paris flight of March 22–23. The last case (patient D) was the manager of the hotel where patient A stayed in Hanoi. He became ill on April 1, a total of 3 days after returning to Vietnam on March 29 through another flight. He had had close contact with patient A on March 22 while greeting and giving him his mail before departure (Figure 1). No other exposure to cases of probable SARS or places where transmission of SARS had occurred in Hanoi could be documented for patient D within 10 days of symptom onset.

Seven persons sat within two rows of patient A during the AF 171 flight (Figure 2), two of whom were medical doctors and did not know him. They indicated that patient A was breathing rapidly (superficial polypnea) and exhibited extreme pallor and pursed lips during the entire flight. He remained calm, had no cough, and left his seat at least twice between Bangkok and Paris to go to the front lavatory; at each move, he passed through the space between the plane wall and seat 25K (Figure 2). During the stopover in Bangkok, he disembarked with the passengers on the flight from Hanoi to Bangkok and then reboarded the plane before the passengers who embarked in Bangkok. On landing at Charles de Gaulle (CDG) Paris Airport, he disembarked among the last passengers (about 20 passengers left the plane after him) and was cared for by the CDG medical services along with two other physicians who had worked in the French Hospital in Hanoi and were on the same plane.

Of the seven passengers who sat within two rows of patient A, SARS developed in one (patient B, seat 25K), which accounted for an incidence density rate of 1 per 100 person hours of exposure (1/98 hours; 95% CI 0.02 to 5.4). He reported having handled the same aircraft magazines and using the same lavatory as patient A (WC1, Figure 2). Within 10 days of onset and while in Hanoi, patient B did not report any contact with the French hospital, other hospitals, or with any SARS patients, nor did he stay at the same hotel as patient A. Another passenger who sat near patient A (26K) reported a sore throat and a temperature of 37.6°C once during follow-up.

The second patient (patient C) sat in seat 30B. He boarded the plane in Bangkok and did not know patient A and did not recall having had any interaction with him during the flight. He used the toilets to the rear behind his seat while patient A used the toilets nearest his seat up front (Figure 2). He was among the first passengers leaving the plane. He did not report any contact with ill persons or hospitals while in Thailand.

Other contacts of patient A included two persons who shared the same car to the Hanoi airport, one of whom had met him for 2 hours before departing; two physicians who had worked in the Hanoi French hospital and left the plane with him; and four healthcare workers of CDG medical services who cared for him. Two taxi drivers (one 1 1/2-hour drive from CDG to his home and one 1/2-hour drive from his home to the infectious disease hospital where he was admitted) were also exposed to patient A, who was then wearing a mask. None of these nine persons had any symptoms during the 10 days after exposure.

SARS did not develop in any of the 30 unprotected persons who had contact with the three secondary confirmed cases after their onset of fever (duration of contact <1/2 hour to 3 days; <2 hours for 26 [86.7%]). However, a febrile illness for 2 days, with no other symptoms, developed in a household contact of patient D, who had a close unprotected contact with him for about 1/2 hour at onset of his symptoms (malaise and fever); a chest x-ray was normal and lymphocyte count was 441/mm^3. RT-PCR on nasal and pharyngeal swab was negative for SARS-CoV. Three healthcare workers who cared for patient D and used masks for droplet protection had brief episodes

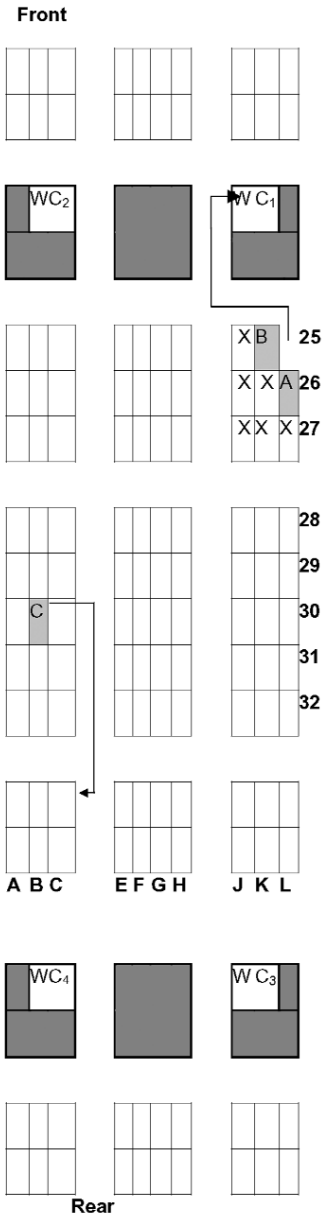

Figure 2. Seats occupied by Probable case-patients with SARS and close contacts to patient A, Air France Flight 171, Hanoi-Paris, 22-23 March, 2003. Numbers and letters in bold indicate seat lanes and rows, respectively. Patient A occupied seat 26L (next to the window). Seats of close passengers who were followed-up for 10 days are indicated by an X. They included two passengers who sat in the row ahead (25K and 25J, there was no seat at 25L), two passengers who occupied seats 26K and 26J, and three passengers who sat in the row behind (27J, 27K, and 27L). A row with no seats separated row 27 from row 28; a partition separated row 25 from the rest of the cabin. Consequently, passengers seated in rows 28 and 24 were excluded. The lavatories are indicated (WC). Patients A and B used the front lavatory (WC_1) while patient C used the one in the back (WC_4). The arrow between seat 26L and the lavatory WC_1 indicates that patient A passed through the empty space between the plane wall and seat 25K where patient B was seated.

(<24 hours) of mild fever without any respiratory symptoms and chest x-ray changes. These three episodes were attributed to a common, unidentified, local viral infection.

Discussion

The surveillance system was able to detect the first patient with SARS (patient A) and one of his secondary case-patients (patient D). Follow-up of passengers seated within two rows of patient A, and the information given to the other passengers of flight AF171 flight allowed patients B and C to be identified. Therefore, all case-patients were identified early in the course of the disease and placed under isolation, which contributed to reduction in the risk of secondary transmission and diffusion (16). Only four of the five probable cases were confirmed either by RT-PCR or serologic testing, although all five met the probable SARS case definition. Although specific, the sensitivity of the RT-PCR–based detection technique remains to be fully evaluated (7). In addition, the time at which respiratory specimens were taken could account for the fact that virus shedding remained undetected for one patient (patient D).

Of the persons who came into contact with a symptomatic SARS patient in France, 30 did not have masks for droplet protection and were exposed, and 26 (86.7%) were exposed for a limited amount of time at the onset of illness. No probable case of SARS was identified among these persons; a household contact of patient D had a febrile illness (>38°C) without any other symptoms and tested negative for the SARS-CoV by RT-PCR. Four contacts of SARS cases had an episode of transient, mild or low-grade fever without other signs, including three healthcare workers of the hospital where patient D had been admitted and the passenger seated next to patient A during the AF171 flight. Specific antibody testing will be the only way to evaluate if these persons with mild symptoms could have been infected by the SARS-CoV.

Since no other exposure could be found within 10 days of onset for patients B and C, their probable source of infection is contact with patient A while in flight, boarding, or disembarking flight AF 171. For patient B, we cannot formally exclude an unrecognized community exposure in Hanoi during the 10 days before departure. However, the fact that the SARS outbreak was controlled quite rapidly (17), without any formal documentation of community transmission, a large unrecognized community transmission most likely did not occur. Patient B, in addition to sitting within two rows of patient A, had contact with patient A when he moved to and from the lavatory (at least four close contacts while going and coming at least twice from the lavatory). Although a precise date of fever onset is not available for patient A, it appears that he was already symptomatic in the plane and was likely infectious. This

finding is based on the following evidence: 1) some persons who had met him in Hanoi before his departure reported that he had fatigue and fits of cough; 2) the passengers closest to him on the plane reported that he was dyspneic; and 3) his initial evaluation at admission to hospital on March 23 showed bilateral extended interstitial pneumonia and hypoxemia. The last strongly supports the hypothesis that his illness was ongoing for 3 to 8 days (1,5,8).

For patient C, the exact mode of acquisition of SARS remains a matter of debate, since he was neither found to have close contact with patient A nor other documented exposure. He had been traveling to Thailand, a country where local transmission has never been reported by WHO (18). Although airborne transmission on the plane cannot be ruled out, a possible hypothesis is an undocumented direct or indirect contact with patient A while boarding or on the plane. Our investigation also indicates that the risk for acquiring SARS after a contact with a symptomatic case is very heterogeneous, since prolonged contact does not necessarily result in transmission and, conversely, a brief or distant exposure might be sufficient. Factors that may explain this observation are the following: 1) the virus excretion varies over time, 2) the susceptibility to the SARS-CoV may vary among persons exposed, and 3) exposure results in asymptomatic infection.

Although our study is descriptive and was not designed to evaluate SARS control measures, our results support the usefulness of recommendations made to prevent the propagation of SARS through air travel (i.e., that persons suspected to have SARS should not fly [14]). We also believe that timely and sensitive surveillance associated with prompt and strict isolation of cases and quarantine of contacts were effective public health tools to limit the secondary spread of SARS in France.

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SARS Outbreak, Taiwan, 2003

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We studied the severe acute respiratory syndrome (SARS) outbreak in Taiwan, using the daily case-reporting data from May 5 to June 4 to learn how it had spread so rapidly. Our results indicate that most SARS-infected persons had symptoms and were admitted before their infections were reclassified as probable cases. This finding could indicate efficient admission, slow reclassification process, or both. The high percentage of nosocomial infections in Taiwan suggests that infection from hospitalized patients with suspected, but not yet classified, cases is a major factor in the spread of disease. Delays in reclassification also contributed to the problem. Because accurate diagnostic testing for SARS is currently lacking, intervention measures aimed at more efficient diagnosis, isolation of suspected SARS patients, and reclassification procedures could greatly reduce the number of infections in future outbreaks.

On April 22, 2003, the World Health Organization (WHO) reported 3,947 probable severe acute respiratory syndrome (SARS) cases with 229 deaths worldwide (1); China, Hong Kong, Singapore, Vietnam, and Toronto, Canada, had the most cases. At that time, Taiwan had 29 probable cases and no deaths. Seventy-eight percent of its cases were imported, and the growth seemed to be exponential but at a comparatively slow rate (2), typical of a minor outbreak. A new cluster of seven infections in Hoping Hospital in Taipei was reported on that day (3), however, starting a chain of local transmissions that cumulated in 116 probable cases and 10 deaths in a fortnight. In the days that followed, the numbers grew to 264 cases and 34 deaths by mid-May, and 680 cases and 81 deaths by June 1—more than a sixfold increase in <l month.

Many questions arose as to how SARS was able to spread so rapidly in Taiwan, a full 2 months after the global alert posted by WHO and >1 month after its passage through Hong Kong, Singapore, and other neighboring countries (4). Inexperience at containing outbreaks and the lack of expert assistance from WHO, at the least at the beginning (5), certainly contributed to the problem. So did inadequacies in the health infrastructure, hospital mismanagement, and simple human carelessness. Hsieh and Chen (2) observed that the cumulative number of probable cases exhibited seemingly random variations in the period after April 22, a feature that cannot be captured by simple curve-fitting techniques. We studied the waves of infections that occurred in most of May by using a mathematical model tailor-made to the specifics of the SARS outbreak in Taiwan but simple enough to allow researchers to draw inferences.

Riley et al. (6) and Lipsitch et al. (7) used dynamic models to model the respective transmission dynamics of SARS in Hong Kong and Singapore. The models were complex and general dynamic models, and they allowed researchers to calculate numerous epidemiologically important parameters and assess the potential danger of the epidemic. Many questions remain, however, such as the effect of data quality on results and the role of heterogeneity in disease transmission (8). We aimed to circumvent problems in answering these questions with a simple mathematical model useful to our understanding of the outbreak.

Methods

We proposed a dynamic model to reflect the actual sequence of events for a reported case-patient in Taiwan, from onset to admission at a hospital as a suspected case-patient to either reclassification as a probable case-patient or removal from the suspected SARS category, and finally reclassification from probable case to discharged case or fatality. Our goal was to evaluate the dynamics at work that resulted in rapid epidemic growth during the period observed. We chose to use a discrete difference equation model because the data used are the discrete daily numbers of reported suspected cases, probable cases, and accumulated deaths posted on the Taiwan Center for Disease Control Web site (9).

Starting from the Hoping Hospital cluster in Taipei on April 22, the large numbers of cases reported daily

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(Figure 1) alerted all residents in Taiwan to the danger of SARS, at times to near-panic state. Amid the heightened tension, the health authority tried to enforce stringent measures to contain the outbreak. One measure was reporting, admitting, and hospitalizing all persons suspected of having SARS. Another was the house quarantine of tens of thousands of persons, mainly those with contacts to the suspected case-patients and to arrivals from affected areas abroad. The quarantine was frequently broken and yielded only 45 probable cases out of over 131,000 people quarantined (10). However, the suspected case-patients who were admitted to the hospital led to the discovery of many probable SARS case-patients. For most of May, the ratio between the number of probable cases reclassified from suspected cases and those removed from the suspected SARS list was roughly one to one. Therefore, reporting and admitting suspected cases appeared to have worked in identifying SARS cases. Nonetheless, almost 73% of all traceable infections in Taiwan occurred in hospital settings (Chwan-Chuan King, unpub. data). Hence, determining the circumstances under which these infections occurred is of interest.

To this end, we considered a model with susceptible patients (S_n), hospitalized suspected case-patients (H_n), reported probable SARS case-patients (I_n), and the accumulated SARS deaths (D_n). The exposed population was not considered since there had been no documented evidence of transmission before onset of symptoms (11). Persons suspected of having SARS were admitted when they had onset of some symptoms combined with a record of recent exposure. Such admission procedures, as well as the protocols for reclassification and downgrading of cases, were carried out in compliance with WHO standards. The flow diagram of the model dynamics is given in Figure 2. The details of the model, including the assumptions made, model equations, and the model parameters, are given in Appendix 1.

We used the daily cumulative numbers of reported suspected cases, probable cases, and deaths from May 5 to June 4 for the true data for the respective numbers for H_n, I_n, and D_n in our model. We chose the data period May 5–June 4 for expediency: it was the only period when all three numbers could be extracted from the Taiwan Center for Disease Control Web site data. We purposely used the number of probable cases by reporting date instead of by onset date to capture what truly happened clinically and in hospital at various stages of a patient's clinical progression.

To simplify our estimation procedure, we discarded the time dependence (or subscript n) of each parameter, thus considering the parameters as mean estimates of the variable parameters over the period considered. The model equations were simplified to a linear system of simultaneous difference equations with which data can be easily implemented for the parameter estimation procedure. We used the three-stage least squares (3SLS) procedure commonly used in econometrics, which provides a useful parameter estimation procedure for simultaneous equations (12). The details of the estimation method are again given in Appendix 2.

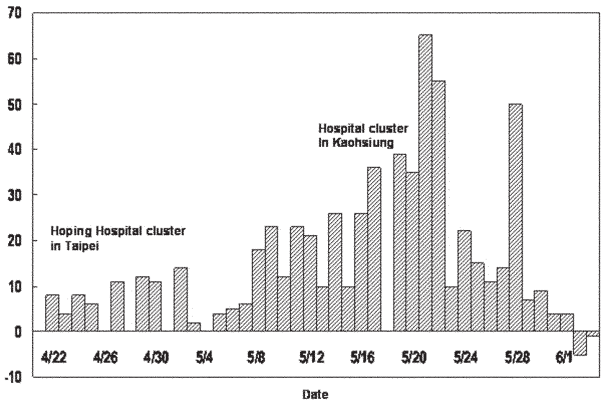

Figure 1. The number of new probable cases in Taiwan by reporting date, April 22-June 4, 2003.

Results

The parameters estimated, without the subscripts, are: λ and β (the respective admission rates due to contact with probable and suspected case-patients at time n-3); ξ (admission rate due to contact with probable case-patient at time n); α (rule out rate of uninfected hospitalized persons at time n); γ (reclassification rate of suspected SARS case-patients to probable at time n); σ (discharge rate of probable SARS patients at time n); ρ (death rate of probable SARS patients at time n). Note that, by their definitions, α, γ, σ, and ρ are proportions between 0 and 1.

From the estimation results, the contributions of contacts of probable case-patients to the suspected SARS

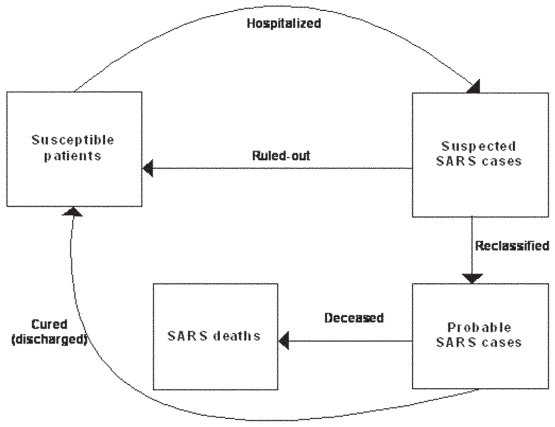

Figure 2. Flow diagram for the model dynamics of the model proposed.

population (λ and ξ) are not significantly different from zero. Hence, almost all SARS-infected persons had symptoms and were admitted before their infections were reclassified from suspected to probable SARS. This finding could indicate efficient admission, slow reclassification process, or a mixture of both. The high percentage of nosocomial infections in Taiwan (73% of all traceable cases) suggests that infection from hospitalized suspected case-patients while they waited to be reclassified (and were subsequently placed in negative-pressure rooms) is a major factor in the spread of disease. Most of the newly admitted suspected case-patients were found by onset of symptoms combined with record of contact with other suspected cases of ≥3 days before (i.e., H_{n-3}). We also attempted to fit the data for possible contacts with I_{n-k} and H_{n-k} for k = 1 to 7 (given that the incubation time has been estimated at 2 to 7 days). Only H_{n-3} turned out to be a significant source of contact for the suspected case-patients. This finding gives a time from infection to onset of ≥3 days.

The results of the parameter estimations are given in Table 1 with the 90% confidence interval (CI) and p value, when appropriate. ρ and β are estimated directly from our estimation procedure of the simultaneous equations with the 90% CI and p values. σ, along with the 90% CI and p value, is obtained through an estimate of $1-\rho-\sigma$; γ is computed from estimate of $\gamma\delta$. α is calculated from the estimate of a product involving δ, γ, and α, from which the 90% CI and p value cannot be easily obtained. The mean proportion of SARS-infected persons among suspected case-patients δ over the period was obtained by using the fact that during the period observed, 1,175 suspected cases were under review. Of these, 562 were reclassified as probable and 613 removed from the category of suspected cases. So we let $\delta = 562/1175 = 0.4783$. The p values indicate that the quality of model fit is good. The numbers computed from the model were plotted against the real data in Figure 3A-C.

To make the results more transparent, we used the mean estimates of daily rates to calculate the mean interval for progression through various stages, given in Table 2. The time from admission to reclassification as a probable case is estimated as $1/\gamma$; time from admission to removal from suspected SARS case list is $1/\alpha$; time for classification as a probable case to death is $1/\rho$ multiplied by 0.15, the overall case-fatality rate of SARS patients, as estimated by WHO; the time from probable case to discharge is $1/\alpha$ multiplied by 0.85, the cure rate.

Discussion

In our study, the gap between mean time from admission to reclassification as probable SARS case-patient was 12.56 days; and the mean time from admission to a case's being ruled out as a SARS case was 2.11 days. When first admitted with symptoms, a patient is treated with an antimicrobial drug. When the symptoms subsequently subside, the patient status is usually downgraded and the patient is removed from the category of suspected SARS case-patients after a few days of observation. Moreover, anyone who is symptomatic, had contact with this person, but shows no lingering symptoms will also be subsequently quickly downgraded. Hence, a mean estimate of 2.11 days from admission to being ruled out as a case seems reasonable. On the other hand, if the antimicrobial treatment does not yield marked improvement, a person is kept under observation for ≥7 days, when either lung x-rays or other tests (antibody test or polymerase chain reaction) will determine if the patient's case should be reclassified as probable SARS. The mean of 12.56 days suggests some delay, either in the cross-checking of diagnostic test results or in the reporting procedure. Confusion regarding case definition and diagnostic procedure (13) might also contribute to the delay. The mean time from classification of a case as probable to death is 24.31 days, implying a mean admission to death time of 36.87 days. The estimate is slightly higher than that for Hong Kong estimated by Donnelly et al. (14) (Table 3). However, this quantity is highly correlated to how quickly a person with onset of symptoms is admitted. As demonstrated with the Hong Kong data (14), the maximum likelihood mean time from onset to admission decreased as the epidemic progressed, probably reflecting a heightened alertness in the general public as well as the health profession. Given the near-panic in Taipei evident from the end of April to most of May, many infected persons (and many non-SARS

Table 1. The model parameter values with 90% confidence interval (CI) and p values, when appropriate[a]

Parameter	Estimated value	90% CI	p value
SARS[b] death rate	ρ =0.0062	0.0023 to 0.00101	0.0125
Discharge rate of probable case-patients	σ =0.0747	0.000[c] to 0.1500	<0.0001[d]
Admission rate of suspected case-patients	β =0.3370	0.0814 to 0.5927	0.0336
Reclassification rate from suspected to probable case	γ =0.0797	0.0281 to 0.1311	0.0142[e]
Rule-out rate of suspected cases	α =0.4271	0.3571 to 0.5927	-
Proportion of probable cases in suspected class	δ =0.4783	-	-

[a]All rates are per day.
[b]SARS, severe acute respiratory syndrome.
[c]Max{0,-0.0046}.
[d]p value for $1-\rho-\sigma$.
[e]p value for $\gamma\delta$.

patients as well) were reported and admitted quickly. However, the fact that most of the infections had occurred in hospital settings highlights the inadequacies in hospital management during this period to effectively isolate suspected SARS case-patients, and instead allowing the spread of SARS to medical staff, other patients, and visitors to the hospital wards.

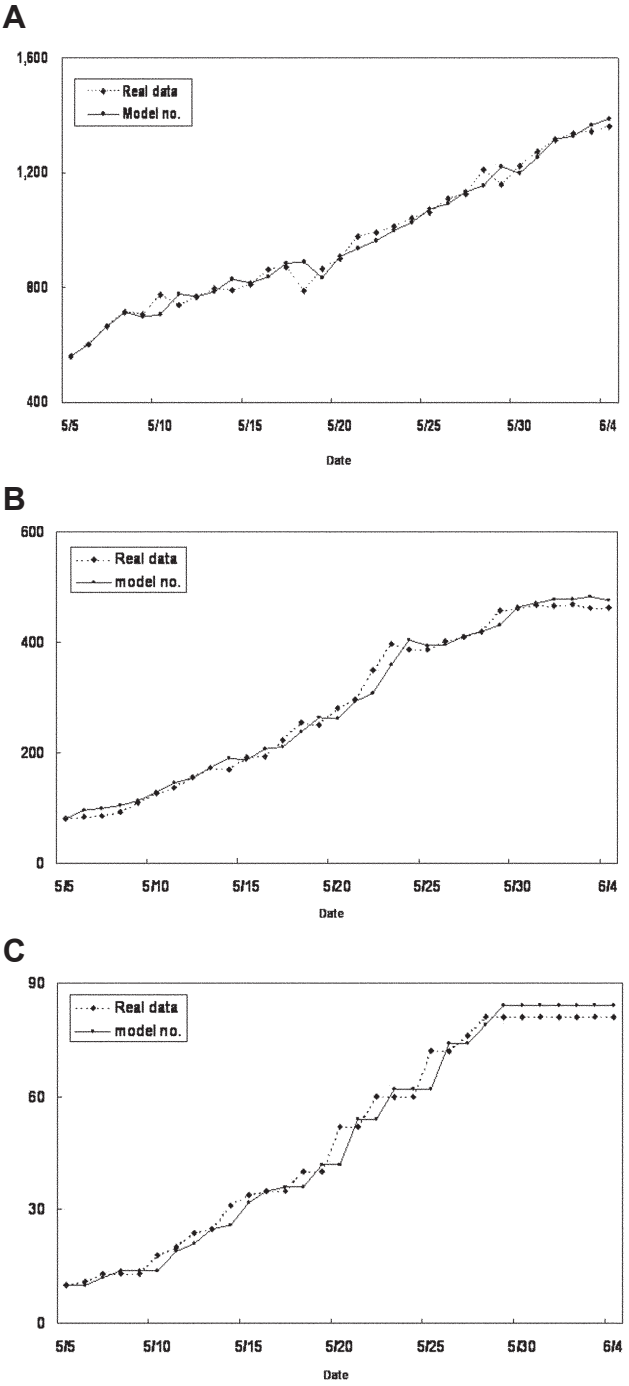

Figure 3. A, number of hospitalized suspected case-patients (H_n) computed from the model compared with real data from May 5 to June 4, 2003. B, number of reported probable case-patients (I_n) computed from the model compared with real data from May 5 to June 4. C, cumulative number of deaths due to severe acute respiratory syndrome (D_n) computed from the model compared with real data from May 5 to June 4.

Table 2. Estimated intervals of epidemiologic importance for SARS outbreaks, Taiwan, May 5–June 4, 2003[a]

Interval for:	Mean estimate (days)
Admission to reclassification as probable case-patient	12.56
Admission to removal from suspected case-patient category	2.11
Probable case classification to death	24.31
Probable case classification to discharge	11.38

[a]SARS, severe acute respiratory syndrome.

Table 3. Comparison of the estimated intervals from admission to death or discharge for SARS patients in Taiwan with those from Hong Kong study[a]

	Days	
Interval for:	Taiwan	Hong Kong
Admission to designation as a probable case-patient to death	36.87	35.9
Admission to designation as a probable case-patient to discharge	23.94	23.5

[a]By Donnelly et al. (13). SARS, severe acute respiratory syndrome.

The total time from admission to discharge for a SARS patient was 23.94 days. To obtain a "mean effective reproductive number for the observed time period," R*, we use the mean admission rate by suspected cases (β) and multiply it by the mean time the person spent as a suspected case-patient before reclassification (12.56 days) to get R* = 4.23. However, this figure might be an overestimate because of uncertainty regarding how infectious a SARS patient is, relative to the change in his or her viral load (15). Note also that the term "mean" refers to averaging over the observed period, to distinguish from the effective reproductive number at time t, R_t (6,7). Figure 1 shows the increases of probable cases in the first 20 days of the period considered, followed by a leveling off of cases. Since β is the effective infection rate of one SARS patient (and also the product of effective contact rate and transmission probability per contact), three factors stood out as critical to any control measure for a SARS outbreak: 1) effective isolation of admitted patients to decrease contact rate, 2) improved safety precautions for hospital staff to lower transmission probability in case of close contact, and 3) shortened reclassification time so that the probable cases-patients can be identified swiftly and put in negative-pressure isolation rooms. A breakdown in any of these measures would lead to temporary failure of the whole system, as witnessed in the outbreak in Taiwan.

Conclusion

The results for the mean effective reproductive number, R*, suggest that the easiest way to reduce infections is more efficient diagnosis of the probable SARS case-

patients and their speedy isolation in negative-pressure rooms. In light of the present lack of accurate diagnostic testing for SARS, public health measures aimed at more efficient clinical diagnosis, isolation of suspected case-patients, and reclassification procedures could greatly reduce the number of infections in future outbreaks. Such steps could be accomplished by quickly identifying the true suspected SARS cases, speedy reporting, effective in-hospital isolation, and fast reclassification of the SARS patients.

The quarantine implemented in Taiwan resulted in only a small number of persons later diagnosed as suspected or probable case-patients. However, one can only speculate about the number of additional infections that the quarantine of these few patients prevented. Events in Canada, for example, demonstrated how one misreported case could lead to an entirely new wave of infections. While there is ample evidence that the quarantine implemented by several countries was instrumental in stopping the spread of SARS, the important public health policy decision of using quarantine as an intervention measure, weighed against its socioeconomic costs, requires further studies with better data and more detailed mathematical modeling.

We had attempted to obtain the estimates by splitting the observed time period into two distinct intervals to see if the three factors involved indeed show a decrease during the course of the observed period. Unfortunately, limited data size inhibits such an endeavor. With the help of Center for Disease Control of Taiwan, more extensive data are currently being collected and generated, including information on the chains of infections as well as clusters. Such data collection takes time, involving the difficult task of contact tracing, but it will form the basis of a more comprehensive modeling study in the future, one that can account for the complete sequence of events.

From the model, it is also clear that the estimated parameters should be time-dependent. However, given the limited data available, one must make simplifications to estimate the means of the parameters over the observed period. With more and better data, one could perhaps estimate the parameters over smaller periods of interest during the complete progression of the epidemic, if not the parameter values for each time n.

Another crucial factor in the outbreak is spatial heterogeneity (i.e., diversity in spatial dimension, brought on by the factor of distance). As Hoping Hospital was closed on April 24 in the aftermath of cluster infections, its patients were allowed to disperse freely to other hospitals; some transferred though the medical system, others on their own. This dispersal of infected persons was directly responsible for several hospital cluster infections in Taipei and even one in Kaohsiung, the southern port city, the effect of which cannot be examined without introducing spatial heterogeneity into the model. Dye and Gay (8) have presented a lucid argument for the confounding role of heterogeneity in epidemic models. Heterogeneity, regardless of whether in host, transmission, spatial, or any other form, cannot be easily conveyed in a complicated general model. One needs to design specific models with a specifically generated dataset to address specific situations. The spread of SARS thus far has been highly society-dependent: under different social settings, SARS has gained foothold in each country or region in a different way, albeit only shortly, be it Hong Kong, Singapore, Toronto, China, or Taiwan. As a long-term goal, to achieve global eradication of the SARS-CoV, one must understand each distinct pattern of transmission, perhaps by distinct and specific SARS modeling.

Acknowledgments

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The authors were supported by grants from National Science Council (NSC) and Center for Disease Control of Taiwan. This work is dedicated to the men and women of the medical profession everywhere in the world who lost their lives fighting on the frontline in the battle against SARS.

Dr. Hsieh is a professor of applied mathematics at National Chung Hsing University. His primary research interests are focused on mathematical and statistical modeling of infectious diseases epidemiology.

Appendix 1. The Model

Model Variables

S_n – The number of susceptible persons at time t = n.

H_n – The number of hospitalized suspected case-patients at time t = n.

I_n – The number of living probable SARS case-patients at time t = n.

D_n – The cumulative number of SARS deaths at time t = n.

Note that time unit is in days.

Assumptions

A person is moved out of susceptible class only after onset of symptoms and/or having a close contact with a probable case-patient.

An infective person can infect others at either suspected or probable stages.

A hospitalized suspected case-patient is removed from the suspected class either by reclassification to a probable SARS case-patient or by returning to susceptible class with no immunity. (If

there is immunity, one can always add a new class of persons with immunity. For the present model this assumption is not important for our estimation result.)

Parameters

λ_n – Admission rate due to contact with probable SARS case-patient at time n–3.

β_n – Admission rate due to contact with suspected case-patient at time n–3.

ξ_n – Admission rate due to contacts with probable case-patient at time n.

α_n – Rule-out rate of uninfected hospitalized persons at time n.

γ_n – Reclassification rate of suspected SARS case-patients to probable at time n.

σ_n – Discharge rate of probable SARS patients at time n.

ρ_n – Fatality rate of probable SARS patients at time n.

δ_n – Proportion of infected persons among all suspected case-patients at time n.

Note that α_n, γ_n, σ_n, ρ_n, and δ_n are proportions between 0 and 1.

The model equations, which describe the change in the model variables from time n to n+1, are as follows:

$$S_{n+1} = S_n - \lambda_n I_{n-3} - \beta_n H_{n-3} - \xi_n I_n + \alpha_n(1-\delta_n)H_n + \sigma_n I_n$$
$$H_{n+1} = \lambda_n I_{n-3} + \xi_n I_n + \beta_n H_{n-3} + (1-\gamma_n)\delta_n H_n + (1-\alpha_n)(1-\delta_n)H_n$$
$$I_{n+1} = I_n - (\sigma_n + \rho_n)I_n + \gamma_n \delta_n H_n$$
$$D_{n+1} = D_n + \rho_n I_n$$

with

$$S_{n+1} + H_{n+1} + I_{n+1} + D_{n+1} = S_n + H_n + I_n + D_n .$$

The flow diagram for the dynamics is given in Figure 2.

Since the equations for H_{n+1}, I_{n+1} and D_{n+1} involve only H_n, I_n and D_n, we can consider these three equations in a simple model

$$H_{n+1} = \lambda_n I_{n-3} + \xi_n I_n + \beta_n H_{n-3} + [(1-\gamma_n)\delta_n + (1-\alpha_n)(1-\delta_n)]H_n$$
$$I_{n+1} = (1-\sigma_n - \rho_n)I_n + \gamma_n \delta_n H_n$$
$$D_{n+1} = D_n + \rho_n I_n$$

which can be put in the following matrix form:

$$\begin{bmatrix} H_{n+1} \\ I_{n+1} \\ D_{n+1} \end{bmatrix} = \begin{bmatrix} (1-\gamma_n)\delta_n + (1-\alpha_n)(1-\delta_n) & \xi_n & 0 \\ \gamma_n \delta_n & (1-\sigma_n-\rho_n) & 0 \\ 0 & \rho_n & 1 \end{bmatrix} \begin{bmatrix} H_n \\ I_n \\ D_n \end{bmatrix} + \begin{bmatrix} \beta_n & \lambda_n & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} H_{n-3} \\ I_{n-3} \\ D_{n-3} \end{bmatrix}$$

The data for H_n, I_n, and D_n, the respective numbers of admitted suspected case-patients, reported probable SARS case-patients, and SARS deaths, are available for parameter estimation.

Appendix 2. Estimation Method

We treat the linear system of equations above as a multiequation simulation model, which allows us to account for the interrelationship within a set of variables, namely, H_n, I_n, and D_n, which are called endogenous variables in econometrics (11). Two-stage least squares (2SLS) and 3SLS can both provide a very useful estimation procedure for simultaneous equation. However, 2SLS is inefficient when the system of equations contains lagged dependent variables, which account for adjustments that take place over time. We can achieve a gain in efficiency by applying 3SLS. It involves applying generalized least squares estimation to a system of equations, each of which has first been estimated using 2SLS. The 3SLS procedure yields more efficient parameter estimates than does 2SLS because it takes into account the cross-equation correlation.

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Multiple Contact Dates and SARS Incubation Periods

Martin I. Meltzer*

Many severe acute respiratory syndrome (SARS) patients have multiple possible incubation periods due to multiple contact dates. Multiple contact dates cannot be used in standard statistical analytic techniques, however. I present a simple spreadsheet-based method that uses multiple contact dates to calculate the possible incubation periods of SARS.

The appearance and rapid spread of severe acute respiratory syndrome (SARS), caused by a previously unknown coronavirus (SARS-CoV) (1–3), has already had a notable economic and social impact (4,5). SARS has no definitive cure, although hospitalized patients have been empirically treated with combinations of antibiotics, steroids, antiviral drugs (typically ribavirin and oseltamivir), and mechanical ventilation (6,7). No known drug can be used prophylactically, nor is does a vaccine exist. Thus, to stop the spread of the disease, public health officials have to rely almost completely on placing those who may have been exposed to SARS-CoV under quarantine and isolating those with suspected, probable, and confirmed SARS cases.

To make quarantine and isolation as effective as possible, knowing the range of the possible incubation period of SARS is essential. Mathematical modelers also need to know the characteristics of the incubation period to provide estimates of possible spread and model the potential impact of interventions. Many SARS patients often report more than one possible date of contact with another known SARS patient (6,7), however, which results in multiple dates of possible transmission and infection (Table). These multiple dates prevent early detection of a discrete period of incubation for each patient, and thus the data from such patients cannot be used in standard statistical analytic techniques, such as regression analyses (unless the analyst chooses a single incubation period from the possible choices) (8).

I present a simple method that allows a simulation of the frequency distribution, including confidence intervals, of the possible incubation periods (in days) for SARS. The method allows use of data from patients with multiple potential incubation periods. One goal of the method was to keep it simple by using common computer spreadsheet software, allowing for easy replication, extension of the database and results, and rapid dissemination of the method. The method can also be used to calculate when infectious persons are most likely to have transmitted SARS to susceptible persons, even when multiple days of possible transmission exist.

Methods

I used published data reporting possible incubation periods for 17 patients (6,7) plus data from two case-patients in an unpublished database maintained at the Centers for Disease Control and Prevention (CDC). The data illustrate a common problem: many patients have multiple possible incubation periods. I built a simulation model in a standard computer spreadsheet (Excel 2000, Microsoft Corp, Redmond, WA) (see online Appendix; available from: URL: http://www.cdc.gov/ncidod/EID/vol10no2/03-0426_spreadsht.xls). I first listed each possible incubation period for every patient for whom incubation period data were available (Table). Then, for every patient, I assigned a random number generator (function RAND in Excel software) to each possible incubation period. This method is the equivalent of using a uniform distribution to select an incubation period from all possible choices. Using a spreadsheet-based simulation software package (@Risk, Palisade Corp., Newfield, NY), I programmed the spreadsheet to run iterations of the model.

During a single iteration, for each patient, the programmed model selects the incubation period with the highest random number for that iteration. After a single iteration, the program calculates the frequency distribution for the incubation periods. Then, the program assigns another set of random numbers to each possible incubation period and selects and calculates the frequency distribution. After numerous iterations, the program combines all the frequency distributions from all iterations to provide a general frequency distribution. From this final frequency

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Table. Patients with severe acute respiratory syndrome (SARS) and possible incubation periods

Patient source and no.[a]	Possible incubation period of SARS in days																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Canada 1		2	3	4	5	6	7	8	9	10	11	12						
Canada 2	1	2	3	4														
Canada 3	1			4														
Canada 4	1	2	3	4	5	6	7	8	9	10	11							
Canada 5	1	2	3	4	5	6	7	8	9	10	11	12	13	14				
Canada 7			3							10								
Canada 8[b]			3															
Canada 10	1	2	3	4	5	6												
Hong Kong 2		2																
Hong Kong 3		2																
Hong Kong 4						6												
Hong Kong 5		2																
Hong Kong 6	1	2	3	4	5	6												
Hong Kong 7					5	6	7	8	9	10	11							
Hong Kong 8					5	6	7	8	9	10	11							
Hong Kong 9	1	2	3	4	5													
Hong Kong 10		2	3	4	5	6	7											
USA 1						6							13	14	15	16	17	18
USA 2							7	8	9	10	11	12						

[a]Patient source: Canada refers to patients reported in reference 6, Hong Kong to patients reported in reference 7, and USA to patients whose incubation periods were extracted from an unpublished database held at CDC. I used the same patient numbers as used in the published reports.
[b]Patient 9 from the Canadian database (6) was excluded because the possible incubation period was reported as ≤ 29 days. However, even with n = 20, adding patient Canada 9 would mean that possible incubation periods between 19 and 29 days would each have very low frequencies (i.e., <0.01).

distribution, descriptive statistics can be obtained, such as the mean, median, 5th and 95th percentile values. I ran approximately 10,000 iterations, at which point each additional iteration caused the mean and the standard distribution for each possible day of incubation to change by <1%.

Results

The three largest mean frequencies of incubation periods among the patients examined were 2, 3, and 6 days (Figure 1). Incubation periods of 1, 4, 5, and 10 days were the second highest mean frequencies (Figure 1). However, the confidence intervals (5th and 95th percentiles) for most of the potential incubation periods clearly overlapped (Figure 1). This finding indicates that with the given data set, an incubation period of 10 days is almost as likely to occur as an incubation period of 6 days. Using the mean frequency of each incubation period, I constructed a cumulative frequency graph (Figure 2). The 95th percentile is 12 days, with a median (50th percentile) of approximately 4 days.

Discussion

The incubation period for SARS is likely to be varied, with the frequency distribution being nonnormal (Figure 1). Thus, using mean incubation periods for activities such as mathematical modeling will probably result in a misrepresentation of SARS transmission. The type of analysis presented here can help public health officials determine minimum quarantine periods for persons exposed to SARS, who are not yet symptomatic. For example, public health authorities should be aware that in a small percentage of case-patients, the incubation period might be >10 days (Figure 2).

Given that data from only 19 patients were available for this analysis, some caution should be exercised when evaluating the results. Adding or subtracting relatively small numbers of patients can cause estimates such as the 95th percentile of the cumulative frequency to change. More

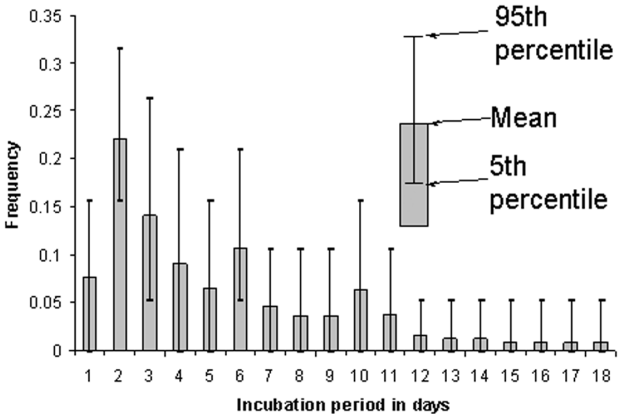

Figure 1. Simulation of frequency distribution of incubation period of severe acute respiratory syndrome. Data used for this simulation were obtained from Canada (6), Hong Kong (7), and the United States, for a total sample size of 19. Many of the patients included in the database had multiple possible incubation periods (see Table), resulting in the confidence intervals displayed for each day.

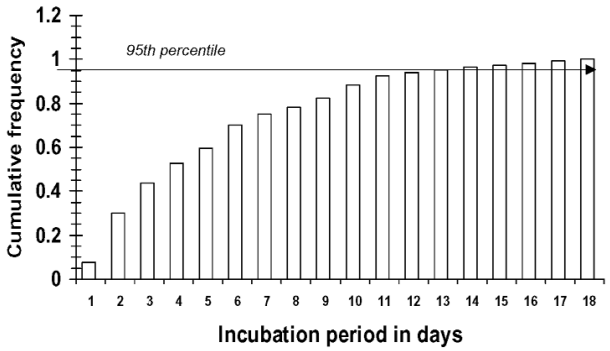

Figure 2. Cumulative frequency incubation period of severe acute respiratory syndrome. Data are the mean frequencies of each individual incubation period, as shown in Figure 1. Data used for this simulation were obtained from Canada (6), Hong Kong (7), and the United States, for a sample size 19. Many of the patients included in the database had multiple possible incubation periods (see Table).

data concerning the possible incubation period of SARS patients are needed. The advantage of the method used here is that such data need not be specific. The method readily "accepts" data in which patients have multiple possible incubation periods. More data will likely reduce the confidence intervals for the frequencies of each incubation day (Figure 1), giving a clearer picture of the actual frequency distribution of all incubation periods.

The method can also be readily adapted to examine other aspects of SARS epidemiology when unambiguous data are scarce. For example, with the appropriate data, this method can be used to examine the frequency distribution of when an infectious person infects other people. (An Excel workbook [Excel 2000, Microsoft, Corp, Redmond, WA] containing the model used to calculate the results shown in Figures 1 and 2, and using the data shown in the Table, is available on line from: URL: http://www.cdc.gov/ncidod/EID/vol10no2/03-0426_spreadsht.xls). Also, distributions of incubation periods can be used to examine whether an association exists between incubation period and likelihood of hospitalization or death.

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Risk Factors for SARS among Persons without Known Contact with SARS Patients, Beijing, China

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Most cases of severe acute respiratory syndrome (SARS) have occurred in close contacts of SARS patients. However, in Beijing, a large proportion of SARS cases occurred in persons without such contact. We conducted a case-control study in Beijing that compared exposures of 94 unlinked, probable SARS patients with those of 281 community-based controls matched for age group and sex. Case-patients were more likely than controls to have chronic medical conditions or to have visited fever clinics (clinics at which possible SARS patients were separated from other patients), eaten outside the home, or taken taxis frequently. The use of masks was strongly protective. Among 31 case-patients for whom convalescent-phase (>21 days) sera were available, 26% had immunoglobulin G to SARS-associated coronavirus. Our finding that clinical SARS was associated with visits to fever clinics supports Beijing's strategy of closing clinics with poor infection-control measures. Our finding that mask use lowered the risk for disease supports the community's use of this strategy.

Severe acute respiratory syndrome (SARS) is a new disease caused by a previously unrecognized coronavirus (1,2). Investigations of SARS outbreaks in several countries suggest that the primary mode of transmission is close contact with a symptomatic patient. Indeed, most cases of SARS have occurred among persons who cared for or lived with someone with the disease, and this fact is reflected in the SARS case definition developed by the World Health Organization and in definitions developed by individual countries (3–7).

The SARS epidemic in Beijing, during which a total of 2,521 probable cases were reported from March through June 2003, was notable for its magnitude (8). Another distinguishing feature was the relatively high proportion of probable case-patients with no reported close contact with other SARS patients. Although the outbreaks in Hong Kong and Toronto were also large, most case-patients had healthcare-related or household links to other SARS patients (4,9). Beijing's epidemic began with importations of SARS-associated coronavirus (SARS-CoV) in travelers returning from Guangdong Province and Hong Kong (8), and the first phase of the epidemic involved hospitalized patients, family members, and healthcare workers exposed to these travelers. During this period (March 8–April 3, 2003), almost all (96%) probable SARS patients reported close contact with a known SARS patient. However, during the peak of the epidemic (April 4–May 4), the percentage of probable SARS patients who reported no contact with another SARS patient and who were not healthcare workers rose to 42%; as the number of cases fell during the last part of the epidemic (May 5–June), this percentage increased to 65%. The reasons for these apparently unlinked SARS cases were unknown. Possible explanations included acquisition of disease from unrecognized sources in the community or healthcare setting, incomplete collection or recording of contact histories, and clinical illness that met the SARS case definition but was caused by etiologic agents other than SARS-CoV.

To evaluate these hypotheses, we conducted a matched case-control study during the Beijing outbreak among a sample of SARS patients who had no reported contact with other SARS patients.

Methods

Definitions

Probable Cases

Probable and suspected SARS cases were defined according to the China Ministry of Health's definitions,

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which included clinical and epidemiologic components. The epidemiologic criteria changed during the course of the outbreak. Before April 3, 2003, only patients who had close contact with a known SARS patient or who had infected other persons could be diagnosed with SARS. From April 4 to May 3, the epidemiologic criteria were expanded to include persons with a history of visiting or residing in cities or areas where local transmission of SARS was occurring or with a history of contact with an outbreak or a healthcare facility. After May 3, Beijing was regarded as having local transmission of SARS, and visiting or residing in Beijing was considered sufficient to meet the epidemiologic criteria of the case definition. Laboratory testing for SARS-CoV was not part of the case definition.

Close Contacts

Close contacts of SARS patients were defined as persons who shared meals, utensils, a residence, a hospital room, or a transportation vehicle with a suspected SARS patient or as persons who visited such a patient in a period beginning up to 14 days before the patient's onset of symptoms. In addition, persons with potential contact with the bodily secretions of a SARS patient during the patient's treatment or care were considered close contacts.

Study Design

A matched case-control study design was used. Case-patients and controls were matched by sex and age group ($\leq$17, 18–25, 26–45, 46–64, and $\geq$65 years). The goal was to enroll 100 case-patients matched with three controls each, which, if one assumes an α of 0.05 and 80% power, would allow detection of an odds ratio of >2.3 for exposures observed in 15% of controls. For the analysis, we excluded all controls <14 years of age because of potential biases in comparing them with matched case-patients aged 14–17 years. In addition, case-patients who were reclassified as healthcare workers after interview were excluded along with their matched controls.

Case-patients were eligible for the study if they met the probable case definition and reported no close contact with any known probable or suspected SARS patients. Only patients whose hospitalization occurred after April 28, 2003, were included in the study. A list of patients admitted to the 16 designated SARS hospitals in Beijing was obtained periodically, and we called patients at the hospital ward or their homes (after discharge) to invite them to participate. The latest date of hospitalization included in our study was June 9, 2003. Case interviews were completed June 3–16.

We selected controls by sequential digit dialing, using the case-patient's home telephone number as the index number. The last digit was added to or subtracted from by one digit in an alternating sequence until three controls matched by sex and age group were enrolled. Telephone prefixes are geographically clustered in Beijing, so this strategy was intended to provide neighborhood matching. Only one control was selected for each number dialed. Control interviews were completed by July 4.

Data Collection

Data from case-patients were collected in person or by telephone, by using a standardized questionnaire. Information was collected on potential risk factors for, or exposures to, SARS-CoV infection (such as having a chronic disease or visiting a healthcare facility), personal hygiene (such as washing hands), and the use of masks. The period of inquiry was the 2 weeks before the patient's onset of symptoms. For case-patients who reported visiting hospitals during the period of interest, a supplemental questionnaire was developed to collect detailed information on reasons for the visits and the hospitals and departments visited. Controls were interviewed by telephone and were queried about a reference period corresponding to the same 2-week period as the matched case.

Trained staff from the Beijing Center for Disease Prevention and Control interviewed all case-patients and approximately half of the controls. To accelerate enrollment, we used a commercial contractor to interview the remaining controls; the contractor received interviewer training by study staff before beginning the interviews. For quality control purposes, 10% of the contractor-interviewed controls were interviewed twice.

Laboratory Tests

Case-patients were asked to come to Beijing Center for Disease Prevention and Control so that a 5-mL blood specimen could be obtained. Blood samples were centrifuged, and serum samples were refrigerated at 4°C. Sera were tested at the Beijing Center for Disease Prevention and Control for immunoglobulin (Ig) G antibody to SARS-CoV, by using an enzyme-linked immunosorbent assay kit (Beijing Huada GBI Biotechnology Co. Ltd., Beijing). All serum samples were obtained $\geq$21 days after illness onset, and 80% of them were obtained 76–106 days after onset of symptoms.

Statistical Analyses

Matched univariate and multivariate analyses were conducted by conditional logistic regression. The PHREG procedure in SAS version 8 (SAS, Cary, NC) was used, with case status as the dependent variable. Factors associated with p values of <0.15 on univariate analysis were included in multivariable models. Collinearity and pairwise interactions were evaluated for all variables in the final model.

Results

A total of 373 patients were called from the master list until 100 were interviewed. Among patients who could be reached, the refusal rate was approximately 50%. The most frequent reasons for refusal were "tired of being interviewed" and being reluctant to disclose any personal information for fear of stigma and discrimination. Patients who agreed to participate in the study were similar in terms of age, sex, and temperature (on clinic presentation) to all probable SARS case-patients without a history of contact with another SARS patient (n = 1,091). Seven controls were excluded because they were <14 years of age, which resulted in the elimination of two matched sets. Four matched sets were also excluded because the case-patient was subsequently reclassified as a healthcare worker. A total of 94 case-patients and 281 matched controls were included in the final analyses.

Male patients accounted for 50% of case-patients. The median age was 29 years (range 14–84) for case-patients and 31 years (range 14–82) for controls. In univariate analyses, several health-related risk factors were significantly associated with an increased risk for clinically diagnosed SARS, including having visited any fever clinic (clinics established to separate patients who might have SARS from other persons being evaluated in emergency rooms or outpatient clinics) or any hospital or having a preexisting chronic disease, such as diabetes (Table 1). Eating out more than once a week and using several types of transportation, including taking a taxi or bus at least once a week, were associated with SARS (Table 1). Having visited a farmer's market, wearing a mask when going out, and washing hands when returning home were protective factors. Factors that were not associated with SARS included visiting a school or university, participating in large social gatherings outside the home, having mice or cockroaches in the home, and having stayed home from work or school. No case-patients or controls reported having traveled to SARS-affected areas, such as Guangdong, Hong Kong, or Toronto.

Factors associated with SARS in multivariable analysis are presented in Table 2. After other factors were controlled for, visiting a fever clinic and having a chronic medical condition remained significantly associated with a risk for SARS. After other variables were adjusted for, having visited a hospital was not associated with acquiring SARS. Other factors associated with an increased risk for SARS were eating outside the home and taking taxis more than once a week. Always wearing a mask when going out was associated with a 70% reduction in risk compared with never wearing a mask. Wearing a mask intermittently was associated with a smaller yet significant reduction in risk. Going to the farmer's market and owning a pet were both protective factors.

As of August 28, 2003, a total of 31 blood specimens had been tested for IgG to SARS-CoV, and 8 (26%) were positive. Of the eight seropositive case-patients, three had not visited a hospital or fever clinic in the 2 weeks before becoming ill.

Discussion

SARS-CoV transmission is now understood to involve close contact of symptomatic patients with others. Surveillance and case management in most parts of the world have focused on patients with clinically compatible illness who had had exposure to another SARS patient or had traveled to an affected area. Once SARS was recognized as widespread in Beijing hospitals, respiratory illness in any Beijing resident raised suspicion of SARS, and health authorities urged a low threshold for consideration of SARS to institute patient isolation, case reporting, and contact tracing. In the Beijing outbreak, the large number of patients who were diagnosed with probable SARS without a contact history led to concerns that overdiagnosis was occurring or, alternatively, that unrecognized sources of transmission existed in the community. Our study suggests that both factors were involved.

Thirty percent of case-patients in this study had a history of visiting a hospital in the 2 weeks before onset of SARS. By univariate analysis, persons with SARS were more than three times as likely as age- and sex-matched controls to have visited hospitals. After other factors, including the presence of chronic medical conditions, were controlled for, visiting a hospital was not independently associated with a higher risk for clinical SARS. The frequency of a history of hospital exposure among our case-patients was consistent with the epidemiology of SARS observed in other major outbreaks, where hospitals served as important amplifiers of transmission. Instituting effective infection-control measures in healthcare settings is the most critical step in controlling the spread of SARS.

Fever clinics were established in Beijing for triage of patients who might have SARS to separate them from other persons being evaluated in emergency rooms or outpatient clinics. Our study found that visiting a fever clinic was a very strong risk factor for SARS. Through a follow-up questionnaire administered to patients who reported having visited hospitals or clinics, we attempted to ensure that the reported visits were for reasons other than the first symptoms of the SARS illness. Our finding that visiting fever clinics increased the risk for probable SARS infection confirms the suspicions of public health authorities that, early in the epidemic response, some fever clinics had not implemented appropriate isolation and triage procedures and supports the public health decision to close dozens of problematic fever clinics and enhance infection-control measures at the 66 clinics that remained open.

Table 1. Selected potential risk and protective factors among cases and matched controls during the 2 weeks before the case-patient's onset of SARS-related symptoms, Beijing, 2003[a]

Potential risk or protective factor for SARS	% of cases with factor N=94	% of controls with factor N = 281	Matched OR (95% CI)[b]	p value
Healthcare related				
Visited any hospital	30	10	3.6 (2.0 to 6.5)	<0.001
Visited any fever clinic[c]	15	1	13.4 (3.8 to 46.7)	<0.001
Having any chronic disease[d]	19	7	4.1 (1.8 to 9.3)	<0.001
Community related				
Visited any school or college	14	16	0.8 (0.4 to 1.6)	0.52
Visited any quarantine site	2	2	1.2 (0.2 to 6.2)	0.83
Attended any social gathering[e]	7	10	0.8 (0.3 to 1.8)	0.52
Visited any movie theater, concert hall, or indoor gym	2	4	0.6 (0.1 to 2.8)	0.48
Visited any farmer's market	23	37	0.5 (0.3 to 0.9)	0.01
Eating out				
Never	62	70	Reference	
Once a week	14	15	1.2 (0.6 to 2.4)	0.67
More than once a week	24	15	2.3 (1.2 to 4.5)	0.01
Riding a bus				
Never	62	73	Reference	
Once a week	13	7	2.3 (1.0 to 5.2)	0.04
More than once a week	25	19	1.7 (0.9 to 3.1)	0.08
Taking a taxi				
Never	80	79	Reference	
Once a week	7	16	0.4 (0.2 to 1.0)	0.05
More than once a week	13	4	3.2 (1.3 to 8.0)	0.01
Taking the subway				
Never	88	91	Reference	
Once a week	1	4	0.3 (0.0 to 2.3)	0.25
More than once a week	11	5	2.5 (1.0 to 6.6)	0.06
Home related				
Did not go to work/attend school	39	40	1.0 (0.6 to 1.6)	0.90
Had a pet	12[f]	20	0.5 (0.2 to 1.1)	0.08
Home infested by rats or mice	10	6	1.6 (0.7 to 3.9)	0.28
Home infested by cockroaches	16	15	1.1 (0.6 to 2.0)	0.87
Behavior related				
Wore a mask when going out				
Never	46	27	Reference	
Sometimes	27	30	0.5 (0.2 to 0.9)	0.02
Always	27	43	0.3 (0.2 to 0.6)	<0.001
Always washed hands before eating	83	89	0.6 (0.3 to 1.1)	0.11
Always washed hands after using restrooms	88	93	0.5 (0.2 to 1.2)	0.10
Always washed hands after returning home	78	90	0.3 (0.2 to 0.7)	0.003

[a]OR, odds ratio; CI, confidence interval; SARS, severe acute respiratory syndrome.
[b]Determined by use of conditional logistic regression. Exposures refer to the 2 weeks before symptom onset for cases and the same 2-week period for matched controls.
[c]Fever clinics were established for triage of patients who might have SARS to separate them from other persons being evaluated in emergency rooms or outpatient clinics.
[d]Includes diabetes, cancer, immunosuppressive treatment, and other.
[e]A gathering of ≥10 persons for a party or other social event.
[f]Pets reported by case-patients included dogs (3 cases), cats (3 cases), fish (1 case), and pigeons (1 case).

In this investigation, persons with chronic medical conditions also had a significantly higher risk of clinical SARS developing. A disproportionate occurrence of the disease in persons who are elderly or who have a chronic disease was noted in other SARS outbreaks, but whether these factors were just markers for persons likely to have nosocomial exposure to other SARS patients was unclear. Our study found that the SARS risk associated with chronic disease was independent of recent exposure to healthcare facilities and suggests that, as is the case for other types of pneumonia (10,11), persons with chronic medical conditions are more vulnerable to clinically defined SARS. We had insufficient numbers of laboratory-confirmed cases to verify that this finding was specific for SARS-CoV infection.

Because a considerable proportion of SARS cases were reported in persons without a history of contact with another SARS patient and without exposure to healthcare facilities, we sought to identify unrecognized sources of community transmission that might help target control strategies and clarify whether widespread community transmission was indeed occurring. We found that certain

Table 2. Factors significantly associated with acquisition of clinically diagnosed SARS in multivariate analysis[a]

Potential risk or protective factor for SARS	Matched OR (95% CI)[a]	p value
Healthcare related		
Visited any fever clinic[b]	12.7 (3.1 to 52.0)	<0.001
Having any chronic disease	4.8 (1.7 to 13.2)	0.002
Visited any farmer's market	0.4 (0.2 to 0.8)	0.01
Eating out		
Never	Reference	
Once a week	1.6 (0.7 to 3.8)	0.3
More than once a week	3.1 (1.2 to 7.7)	0.02
Taking a taxi		
Never	Reference	
Once a week	0.2 (0.1 to 0.8)	0.02
More than once a week	3.0 (0.9 to 10.3)	0.07
Had a pet	0.4 (0.2 to 0.9)	0.03
Wore a mask when going out		
Never	Reference	
Sometimes	0.4 (0.2 to 0.9)	0.03
Always	0.3 (0.1 to 0.6)	0.002

[a]OR, odds ratio; CI, confidence interval; SARS, severe acute respiratory syndrome.
[b]Fever clinics were established for triage of patients who might have SARS to separate them from other persons being evaluated in emergency rooms or outpatient clinics.

community exposures were significantly more common among case-patients than controls, including eating out or taking taxis frequently. By univariate analysis, use of other common transport (e.g., buses, subways) was also associated with a risk for SARS. At least one well-publicized case of SARS in Beijing occurred in a taxi driver (12), but an increased risk among passengers had not previously been documented. Our findings regarding use of transportation bordered on statistical significance and will require validation by other studies.

We also used this investigation to quantify the impact of behaviors (i.e., mask wearing, handwashing) that were promoted to reduce the risk for SARS. Wearing masks outside the home in a reference period corresponding to the 2 weeks before symptom onset for cases was significantly protective against clinical SARS. Supporting the validity of this finding, there was a dose-response effect: by multivariable analysis, persons who always wore masks had a 70% lower risk of being diagnosed with clinical SARS compared with those who never wore masks, and persons with intermittent mask use had a 60% lower risk. Many persons who wore masks in the community did not use N-95 or similar highly efficient filtration devices, which have been recommended for use in the hospital setting. We sought details on the type of masks used but were unable to evaluate the protective efficacy for different mask types. We also were not able to differentiate protective efficacy for SARS-CoV versus efficacy against other pneumonia causes that met the clinical case definition.

Handwashing has been recommended to prevent SARS and other respiratory and diarrheal infections in which contact is an important mode of transmission. We found that consistently washing hands upon returning home was associated with a reduced risk for clinical SARS by univariate but not multivariate analysis. However, self-reported handwashing practices may be particularly prone to misclassification because respondents might provide the answer they believe is expected of them.

We also explored the role of domestic animals in relation to SARS infection among persons without contact with another SARS patient. An animal source for the origin of SARS-CoV in humans is suspected (13), and, using polymerase chain reaction, investigators identified SARS-CoV in household pets and cockroaches at the Amoy Gardens apartments in Hong Kong (14). Thus, we wondered whether certain household pets or rodents might be perpetuating disease-transmission cycles. One investigator recently hypothesized that a rodent vector may have amplified transmission of SARS at Amoy Gardens (15). In addition, rumors circulating during the Beijing SARS outbreak led to some calls for banning household pets or restricting them from common areas. We sought evidence to address this community fear and found that household rodents and cockroaches were not associated with a risk for clinical SARS. We also found that persons with pets had a significantly lower risk for clinical SARS. This finding might have occurred by chance or may be confounded by another factor more directly related to pneumonia. However, controls with pets might possibly have had exposure to other animal coronaviruses that provided cross-reacting antibody to the SARS-CoV. Of note, other investigators found IgG to SARS-CoV was common among animal traders in Guangdong (16), yet disease did not occur in this population, a finding consistent with the hypothesis that cross-reacting antibodies to a closely related virus may have protected these workers.

Another unexpected finding was that visiting a farmer's market was associated with a reduced risk for clinical SARS. Nevertheless, concern that farmers represented travelers from other provinces and that markets were crowded settings prompted us to ask about this exposure as a possible risk factor. Accounting for an association with lower risk is challenging. As with ownership of pets, this finding may relate to unmeasured lifestyle factors more directly related to pneumonia risk.

Among authorities in Beijing, a leading hypothesis for the occurrence of clinical SARS among patients without known contact with another SARS patient was that overdiagnosis was occurring. We sought to determine the proportion of case-patients in this study who could be confirmed by convalescent-phase serologic tests to be infected with SARS-CoV; however, we obtained serum samples

from an insufficient number of case-patients to analyze risk factors for laboratory-confirmed cases. Serologic testing for SARS may not be 100% sensitive, and the Huada test kit has had limited validation thus far. Nevertheless, a substantial portion of case-patients without contact with other SARS patients likely had pneumonia caused by pathogens other than SARS-CoV.

Certain limitations to this study should be mentioned. First, the study was conducted late in the Beijing epidemic, after patients had been hospitalized for several weeks, and the low participation rate might be attributable to patients having already been interviewed multiple times. Furthermore, recall bias might have influenced some of the factors we explored. Telephone-based public health studies were relatively new to Beijing, and the representativeness of our control population is not known. Because the rate of study participation by case-patients was not high, those who agreed to participate may have self-selected for unknown reasons that could have biased our findings. For instance, several patients responding to the open-ended comment section mentioned that they were certain their illness was "not SARS." Relatively few patients agreed to convalescent-phase serologic testing, and those who did agree may have been more skeptical about the cause of their pneumonia than were others, which may have skewed the sample for which we have serologic results.

In conclusion, we identified several explanations for the occurrence of clinically defined SARS in persons without contact with another SARS patient during Beijing's 2003 SARS epidemic. The nonspecific clinical definition for SARS led to reporting of many cases that were not confirmed to be caused by SARS-CoV. This apparent overdiagnosis probably helped ensure rapid control of the outbreak by introducing a wide net for contact tracing and patient isolation. Increased risk for clinically defined SARS was associated with attending fever clinics, having a chronic disease, and having certain community exposures. Consistent mask use lowered the risk for disease, thus providing some justification for the use of a strategy that was very popular in the general community. Our finding that pet owners had a lower risk for clinical SARS can help dispel fears that domestic pets were causing disease transmission in Beijing. Improved laboratory diagnostic tests (i.e., tests with high sensitivity early in the illness and with rapid turnaround) may eventually allow for more specific case reporting and management. Although human-to-human transmission of SARS has apparently been interrupted as of this writing, the factors associated with clinically defined SARS in this study may help target future efforts to control other respiratory infections, including pandemic influenza, and will provide valuable evidence for the control of SARS should the disease return.

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Lack of SARS Transmission and U.S. SARS Case-Patient

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In early April 2003, severe acute respiratory syndrome (SARS) was diagnosed in a Pennsylvania resident after his exposure to persons with SARS in Toronto, Canada. To identify contacts of the case-patient and evaluate the risk for SARS transmission, a detailed epidemiologic investigation was performed. On the basis of this investigation, 26 persons (17 healthcare workers, 4 household contacts, and 5 others) were identified as having had close contact with this case-patient before infection-control practices were implemented. Laboratory evaluation of clinical specimens showed no evidence of transmission of SARS-associated coronavirus (SARS-CoV) infection to any close contact of this patient. This investigation documents that, under certain circumstances, SARS-CoV is not readily transmitted to close contacts, despite ample unprotected exposures. Improving the understanding of risk factors for transmission will help focus public health control measures.

On March 12, 2003, the World Health Organization (WHO) issued a global alert for severe acute respiratory syndrome (SARS) after outbreaks had been recognized in Vietnam, Hong Kong, and the People's Republic of China (1). The outbreak subsequently spread to Singapore, Taiwan, Canada, and elsewhere (2–8). In the United States, laboratory-confirmed SARS-associated coronavirus (SARS-CoV) infection was diagnosed in eight persons (9). Of these eight patients, only one may have been infected in the United States.

"Superspreading events," in which a single person spread the infection to many other people, were an important component of SARS transmission globally. In Singapore and Taiwan, for instance, single case-patients may have transmitted the virus to >60 persons (7,8). However, for most SARS case-patients, transmission was limited; for example, after the institution of intensive infection-control measures in Singapore, 81% of probable SARS patients had no evidence of transmission to other persons (7). By using mathematical models that included epidemiologic data (excluding superspreading events) from Singapore and Hong Kong, two to three secondary infections were estimated to result from single infectious case-patients before infection control measures were instituted (10,11). It is important to systematically assess risk associated with SARS transmission in order to implement effective control measures.

On April 14, 2003, a 52-year-old Pennsylvania resident was recognized as a probable SARS case-patient after his exposure to persons with SARS during a religious event in Toronto in late March (12). Some attendees of this event were infected with SARS-CoV through a chain of transmission linked to the first imported case of SARS in Canada, a woman who had become infected in Hong Kong (13–15). Overall, 20 probable and 11 suspected cases of SARS were identified in this religious community (14); the Pennsylvania patient was the only U.S. case. Before the Pennsylvania patient was recognized as a probable SARS case-patient and infection control practices were instituted, the patient interacted with numerous healthcare workers

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and other persons. We summarize the epidemiologic and laboratory investigations performed to identify persons exposed to the patient and to determine whether any were infected.

Methods

Epidemiologic Investigation

Potential close contacts were identified through interviews with the case-patient, his family members, healthcare workers, and other persons. Additional clinical and contact information was obtained through review of medical records. "Close contact" exposures included any amount of time spent within 3 feet of the patient or 30 minutes or longer within 3 to 10 feet. Since evidence suggests that SARS-CoV is primarily transmitted by means of large respiratory droplets, usually spread within a 3-foot radius, we focused on contact within this range (16). Thirty minutes within the patient's immediate care area (3–10 feet) was chosen arbitrarily to divide shorter and longer exposures.

Contacts included persons exposed to the patient before and after his diagnosis as a probable SARS patient. Contacts were grouped according to sites of principal exposure: the term "healthcare workers" refers to employees or contractors of a healthcare facility, "healthcare-related contacts" includes non–healthcare worker contacts exposed in a healthcare setting, "household contacts" includes immediate family members, whether they resided in the same household or not, and "community contacts" includes persons exposed in other settings. Public health personnel, using standard data collection instruments, interviewed contacts regarding their type and duration of contact with the patient, use of personal protective equipment, and clinical symptoms after contact. Direct, unprotected contact with the patient's skin (i.e., without gloves) was defined as skin-to-skin contact, and unprotected contact with inanimate objects likely to have been touched by the patient, such as bedrails and clothing, was defined as skin-to-object contact.

Contacts were defined as prediagnosis or postdiagnosis contacts. Prediagnosis contacts were those exposed to the case-patient after his onset of symptoms (April 3) but before the patient's diagnosis of probable SARS (April 14). Postdiagnosis contacts were those exposed only after the diagnosis was made and infection control precautions were in effect. A convenience sample of postdiagnosis contacts was selected because strict infection control procedures had already been instituted, with all contacts wearing personal protective equipment; thus, unprotected exposures were not anticipated. Of the 32 persons with postdiagnosis exposure exclusively, 15 healthcare workers were selected for epidemiologic and laboratory evaluation.

Biologic Specimen Collection

Serum, whole blood (collected into a tube containing EDTA), oropharyngeal swab (swab of posterior pharynx), stool, and urine samples were requested from the case-patient twice weekly until day 21 after symptom onset and weekly for 2 additional weeks. In addition, a single nasopharyngeal swab specimen, nasal aspirate, and sputum sample were collected from the case-patient while he was hospitalized. The first set of specimens requested from his prediagnosis contacts included serum, whole blood, nasopharyngeal and oropharyngeal swab specimens, stool, and urine. Thereafter, specimens (serum, whole blood, oropharyngeal swab, and stool) were requested from prediagnosis contacts weekly until at least 22 days after the most recent exposure to the case-patient. Healthcare workers with postdiagnosis exposure submitted a single set of convalescent-phase specimens (>21 days after the last exposure), including serum, whole blood, and an oropharyngeal swab. Nasopharyngeal and oropharyngeal swab specimens were collected by using Dacron swabs with nonwooden handles. Swabs were immediately placed into viral transport medium and placed on ice. All specimens were stored at 4°C and shipped within 72 hours of collection to the Centers for Disease Control and Prevention (CDC).

Two postdiagnosis healthcare workers, in whom fever developed after they were exposed to the case-patient, provided weekly specimens rather than a single set. One prediagnosis healthcare-related contact participated until 22 days after exposure but did not provide serum or whole blood specimens, and four prediagnosis contacts (2 healthcare workers and 2 healthcare-related contacts) declined further participation after specimen collection at 8, 11, 11, and 21 days after exposure, respectively.

Environmental Specimen Collection

Sterile Dacron swabs with nonwooden handles were moistened with sterile saline or viral transport medium and rolled over environmental surfaces, including toilet and sink surfaces and other commonly touched items (e.g., door handles, telephones, remote controls, and toiletries) and placed in viral transport medium. Twenty environmental swab samples were collected from the patient's hospital room during his hospitalization (day 17 after illness onset), and 12 were collected from his home bedroom and private bathroom 3 days after hospital discharge (day 21 after illness onset). These were stored and shipped to CDC at 4°C.

Laboratory Testing

To test for evidence of infection with SARS-CoV, total anti–SARS-CoV serum antibody was measured by enzyme-linked immunosorbent assay (ELISA) and indirect fluorescent antibody test (17). Reverse transcription–polymerase chain reaction (RT-PCR) was

performed on nasopharyngeal and oropharyngeal swabs and stool and urine specimens; results were confirmed in separate CDC laboratories, with both negative and positive controls (17,18). Quantitative RT-PCR on stool specimens was conducted by using the TaqMan assay and standard curves generated from synthetic RNA transcripts (17). Viral culture in Vero E6 cells was performed on all RT-PCR–positive specimens (17).

Human Participants

This investigation was conducted as part of CDC's public health response to the SARS outbreak. Informed consent was obtained from the case-patient and contacts before epidemiologic information was obtained and biologic specimens were collected.

Statistical Analysis

Due to the non-Gaussian distribution of the data, the Wilcoxon rank-sum test was used to compare median durations of contact between different groups of persons. Prevalences of different types of exposures between the groups were compared by using Fisher exact test.

Results

Clinical History and Laboratory Findings for the Case-Patient

After traveling by automobile to an event held in Toronto on March 29 and 30, the previously healthy patient had onset of myalgias, subjective fever, chills, and diaphoresis on April 3 (Figure 1). Diarrhea developed on April 5, and the patient sought medical care at the emergency department of hospital A on April 6. The patient had a temperature of 38.2°C (100.7°F) and was discharged with a diagnosis of acute viral syndrome; no diagnostic testing was performed. During this emergency department visit, the patient did not report recent travel to Toronto to healthcare providers. By April 10, despite taking oral amoxicillin for 3 days (initiated after telephone consultation with his primary care physician), a dry cough developed, which prompted him to visit his primary care physician. His physician referred him to an outpatient laboratory for phlebotomy and to hospital B for chest radiography; findings on the radiograph were normal, and the patient was sent home.

On April 14, the patient went to the emergency department of hospital B with dehydration, worsening cough, and severe shortness of breath. Within 2.5 hours of arrival, a diagnosis of SARS was suspected on the basis of a full travel history and new radiographic evidence of pneumonia. The patient was admitted to an airborne-infection (negative-pressure) isolation room, and the hospital instituted contact and airborne precautions for all healthcare workers

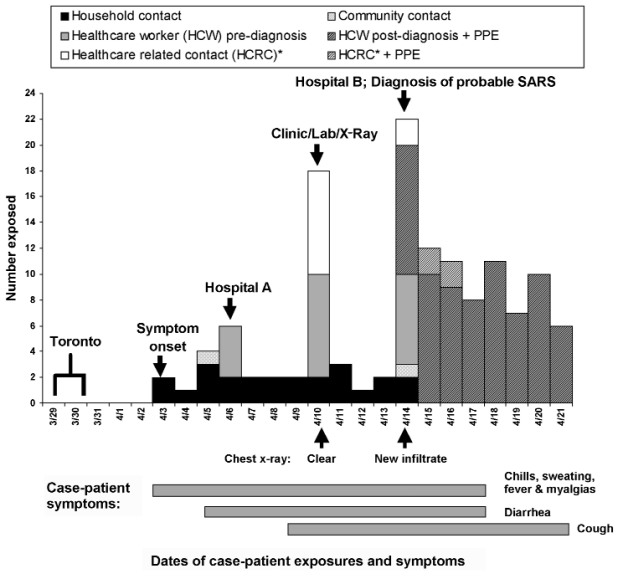

Figure 1. Timeline: severe acute respiratory syndrome (SARS) case-patient symptoms and total daily number of contacts from date of symptom onset to date of hospital discharge. Contacts indicated regardless of their subsequent participation in this investigation. Close contact was defined as any contact within 3 feet or contact within 3 to 10 feet for an extended duration (two persons). Repeated contacts by the same person over successive days are shown as independent events. *Healthcare-related contact refers to non-healthcare worker (HCW) contacts in a healthcare setting (persons in waiting rooms of physician office and referral laboratory, curtained area in the emergency department, and two persons who reportedly used personal protective equipment [PPE] and visited the case-patient in his hospital room on 4/15 and 4/16).

in contact with the patient, restricted visitation to this patient, and immediately notified public health authorities. Serum samples collected on April 14 (day 11 of illness) demonstrated antibodies to SARS-CoV. Admission vital signs included a temperature of 37.7°C (99.9°F) and oxygen saturations of 90%–91% on room air. The patient was given supportive care (including 2 days of supplemental oxygen), inhaled fluticasone propionate/salmeterol twice daily, and antimicrobial drugs (levofloxacin for pneumonia and metronidazole for diarrhea associated with laboratory-confirmed *Clostridium difficile* infection). His highest documented temperature while hospitalized was 38.1°C (100.6°F) on April 15. After the patient was hospitalized for 4 days, his fever and systemic symptoms resolved, and he was discharged on April 21 (hospital day 7) with a persistent but improving cough. He did not require aerosolized nebulizer treatments, intubation, or admission to an intensive care unit during his hospitalization.

The case-patient's serum specimens from days 11 to 32 after illness onset demonstrated anti–SARS-CoV antibodies (Figure 2). Additional analysis showed an increase in antibody titer over time (19). All respiratory specimens and the only urine sample tested negative by RT-PCR for

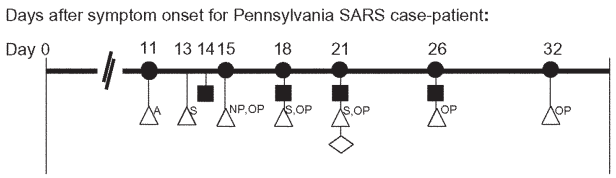

Figure 2. Clinical specimens collected and laboratory results for Pennsylvania severe acute respiratory syndrome (SARS) case-patient, April 2003. Symbols of specimens and method of testing: serum anti-SARS-CoV antibody, ○ ; stool RT-PCR; ■; urine RT-PCR, ◇; and respiratory RT-PCR, △ ; A, nasal aspirate; S, sputum; NP; nasopharyngeal swab; OP, oropharyngeal swab. Black shading indicates laboratory-positive specimen. Viral cultures of all stools and respiratory specimens were also performed and were negative.

SARS-CoV. However, serial stool specimens collected on days 14, 18, 21, and 26 after the onset of illness were positive by RT-PCR. Quantitative PCR showed the copy number in the first collected stool to be 16- to 40-fold higher than that in all subsequent stools (19). Viral cultures of all stools and respiratory specimens were negative for SARS-CoV, and all environmental specimens were negative by RT-PCR for SARS-CoV.

Epidemiologic and Laboratory Results for Contacts

The principal potential exposure sites that were investigated included sites for healthcare worker and healthcare-related contact exposures (emergency department of hospital A; primary care physician's office; referral phlebotomy laboratory; and emergency department, radiology suite, and inpatient facility of hospital B), the patient's home, and community settings in which the patient reported having had close contacts.

Prediagnosis Contacts

Thirty-four potential prediagnosis contacts were identified, and questionnaires were collected from 26 (76%) of them. The eight remaining potential prediagnosis contacts, who did not complete questionnaires, included seven healthcare-related contacts (six who were present in a laboratory waiting room at the same time as the case-patient and one radiology staff member) and one community contact (a retail salesperson). Of these eight persons, two could not be contacted, five did not complete more detailed interviews but did not recall specific interaction with the patient or report any subsequent illness, and one reported brief contact with the patient with no subsequent symptoms and declined to answer further questions.

The 26 prediagnosis contacts who completed questionnaires included 4 household contacts (15%), 17 healthcare workers (65%), and 5 others (19%), including 4 healthcare-related contacts (4 persons in a waiting room or curtained area in the emergency department) and 1 community contact (a bank teller) (Table). The median age of prediagnosis contacts was 41.3 years (range 15.7–90.1); the only 2 contacts over age 65 were healthcare-related contacts.

Of these 26 persons, nearly all (92%) had contact with the patient during the 3 days when he sought medical care (Figures 1, 3). All household contacts and healthcare workers with prediagnosis contact had close unprotected exposures (within 3 feet), compared with 40% of the other contacts; this finding was significantly different only for healthcare workers ($p = 0.006$; $p = 0.17$ for household contacts) (Table). However, household contacts had the longest median duration of exposure per person, 60 times longer than the median duration per person among prediagnosis healthcare workers (459 vs. 7.5 minutes, $p = 0.04$) and 15 times longer than among other contacts (459 vs. 30 minutes, $p = 0.008$). Household contacts and healthcare workers had similar degrees of skin-to-skin contact (50% vs. 53%, $p = 1.00$) and skin-to-object contact (100% vs. 71%, $p = 0.53$). The patient and household contacts attempted to limit interactions throughout his illness and began wearing surgical masks when they interacted after April 9.

All contacts were monitored for fever and respiratory symptoms during the 10 days after exposure to the case-patient. Eleven (42%) of the 26 prediagnosis contacts reported fever and/or lower respiratory tract symptoms (defined as cough, wheezing, or shortness of breath/difficulty breathing) during the surveillance period. Of the 26, 1 (4%) reported fever alone, 9 (35%) reported respiratory symptoms alone, and 1 reported both. The person with both fever and respiratory tract symptoms was a household contact who reported sore throat and cough before contact; fever developed after contact, thus meeting the CDC clinical case definition for a suspected SARS case (9,20). Seven (41%) of 17 healthcare workers with prediagnosis contact were furloughed from work for 3 to 10 days due to unprotected close contact or the presence of respiratory symptoms. Four (57%) of these persons had lower respiratory tract symptoms, and three (43%) were asymptomatic or had only mild symptoms (sore throat, headache, or rhinorrhea).

Prediagnosis contacts provided a total of 86 serum and whole blood samples, 90 oropharyngeal swabs, 25 nasopharyngeal swabs, 18 stool samples, and 4 urine specimens (Table). The household contact who met the suspected SARS case definition provided a single nasopharyngeal swab, stool, and urine samples, and acute- and convalescent-phase (37 days after contact) serum specimens, whole blood samples, and oropharyngeal swabs. The other contact with fever provided a single nasopharyngeal swab and stool sample and three oropharyngeal swabs, serum specimens, and whole blood samples (up to 22 days after contact). The median time after contact to

Table. Characteristics of contacts of SARS case-patient—Pennsylvania, 2003

Variable	All contacts (N = 41) (%)	Prediagnosis[a]			Postdiagnosis[a] healthcare workers (n = 15) (%)
		Healthcare workers (n = 17) (%)	Household contacts (n = 4) (%)	Other[b] (n = 5) (%)	
Age (y)					
≥50	9 (22)	4 (24)	0	3 (60)	2 (13)
18–49	31 (76)	13 (77)	3 (75)	2 (40)	13 (87)
<18	1 (2)	0	1 (25)	0	0
Male	10 (24)	4 (24)	1 (25)	2 (40)	3 (20)
No. minutes of total contact per person, median (range)	28 (1–741)	7.5 (1–30)	459 (241–741)	30 (10–150)	110 (10–280)
Types of contact,					
Within 3 feet	38 (93)	17 (100)	4 (100)	2 (40)	15 (100)
Skin to object	17 (41)	12 (71)	4 (100)	1 (20)	0
Skin to skin	13 (32)	9 (53)	2 (50)	1 (20)	1 (7)
Use of PPE[c]	13 (32)	0	0	0	13 (87)
Postexposure symptoms[d]					
Fever	4 (10)	0	1 (25)	1 (20)	2 (13)
Respiratory symptoms	11 (27)	7 (41)	1 (25)	2 (40)	1 (7)
Met case definition (suspect case)	2 (5)	0	1 (25)	0	1 (7)
Furloughed from work, no. (%)	11 (27)	7 (41)	2 (50)	1 (20)	1 (7)
Total no. of specimens collected (average/person)					
Serum	125 (3)	63 (3.7)	14 (3.5)	9 (1.8)	39 (2.6)
Nasopharyngeal swab	35 (0.9)	17 (1)	4 (1)	4 (0.8)	10 (0.7)
Oropharyngeal swab	124 (3)	64 (3.8)	14 (3.5)	12 (2.4)	34 (2.3)
Stool	21 (0. 5)	10 (0. 6)	3 (0. 8)	5 (1)	3 (0.2)
Urine	4 (0.1)	0	4 (1)	0	0
No. of days from last contact to last serum collection, median (range)[e]	28 (8–37)	28 (8–29)	29 (28–37)	16.5 (11–28)[e]	25 (22–30)

[a]Prediagnosis contacts were those exposed to the case-patient after his onset of symptoms (April 3, 2003) but before his diagnosis with probable severe acute respiratory syndrome (SARS) (April 14). Postdiagnosis contacts were those exposed only after the diagnosis was made and infection control precautions were in effect.
[b]Other, 4 contacts with healthcare–related exposure and 1 community exposure.
[c]N95 respirator, gown, gloves. To be counted as having worn personal protective equipment (PPE), contact had to have worn it for every interaction with the case-patient.
[d]Symptoms occurring during the 10-day period after contact with the case-patient.
[e]Median and range for "other" category is for 4 contacts, since 1 contact did not provide any serum specimens.

collection of the last serum specimen was 28 days (range 8–37). All specimens tested negative for SARS-CoV.

Postdiagnosis Contacts

Some contacts had unprotected exposures within 3 feet on the day SARS was diagnosed in the case-patient; the most prolonged of these were 210 minutes for a household contact and 30 minutes, including skin-to-skin contact, for a community contact (Figure 3). However, nearly all contacts were protected after diagnosis (Figures 1, 3; Table). The sample of 15 postdiagnosis healthcare workers was protected with fit-tested N95 respirators, gowns, and gloves (goggles were added on day 2 of hospitalization). Postdiagnosis healthcare workers had a median age of 39.1 years (range 24.6–51.7). Despite much longer median durations of exposure compared with those of the prediagnosis healthcare workers (110 vs. 7.5 minutes/person, $p<0.005$; Table), postdiagnosis healthcare workers had only two unprotected close contacts, one failure to wear a gown, and one failure to wear an N95 respirator and gloves during skin-to-skin contact.

After contact with the patient, two (14%) postdiagnosis healthcare workers reported fever. One of these persons also reported a cough 2 days after exposure to the case-patient and, therefore, met the clinical case definition for suspected SARS (9,20). This person was admitted to the hospital for 1 night with a diagnosis of respiratory syncytial virus infection (antigen-positive nasal aspirate) and asthma exacerbation. Neither of these symptomatic postdiagnosis healthcare workers had breaches in personal protection equipment. All specimens from postdiagnosis healthcare workers tested negative for SARS-CoV, including specimens from both contacts with fever, each of whom provided a single nasopharyngeal swab and weekly oropharyngeal swabs, serum specimens, and whole blood samples (up to 27 and 28 days after contact).

Discussion

This investigation provides the first detailed epidemiologic analysis of persons exposed to a U.S. patient with serologically confirmed SARS. Despite substantial contact with many persons, this case-patient did not transmit SARS-CoV, which is in contrast to experiences in Singapore (7), Taiwan (8), and Canada (15), where in some circumstances, limited contact to some case-patients led to many secondary infections. Similar lack of transmission

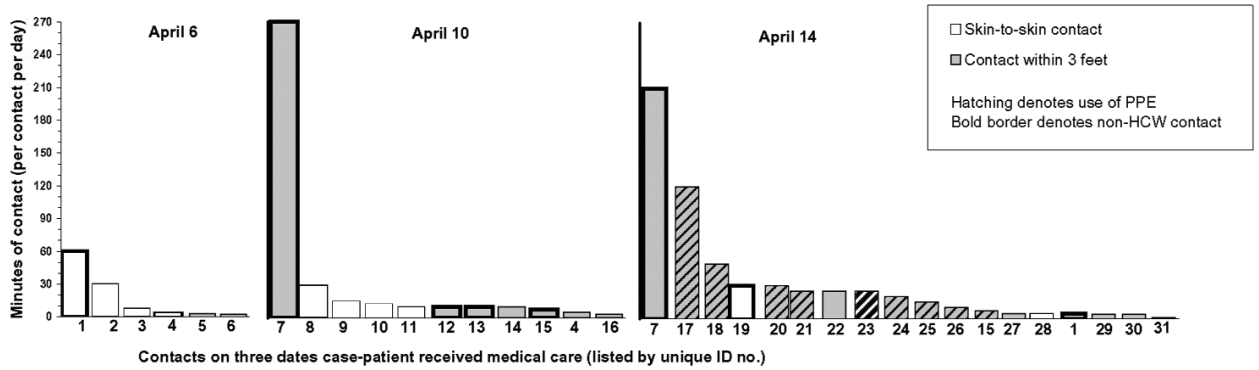

Figure 3. Duration of exposure for close contacts within 3 feet on the three dates when the case-patient with severe acute respiratory syndrome sought medical care. Four contacts (three household contacts and one healthcare worker) had contact with the patient on 2 of these days. Two healthcare workers had both protected and unprotected contact (shown with hatching).

from probable SARS case-patients has been documented in other settings (7); however, detailed exposure data have not been provided. Our findings demonstrate that in certain situations, even in the context of prolonged close contact without use of personal protective equipment, SARS-CoV may not be transmitted.

Certain aspects of this case-patient's illness may account for the lack of transmission. The case-patient did not have a cough until almost 1 week after symptom onset, and his respiratory secretions were negative for SARS-CoV by RT-PCR 11 days after symptom onset, although his stool specimen remained positive by RT-PCR for 26 days. In a report of the Hong Kong outbreak, viral RNA was identified in 68% of nasopharyngeal aspirates by the second week of illness (21); one interpretation of the negative results in this case-patient is that virus load in respiratory secretions may have been low. In addition, although the patient's stool specimens were positive for SARS-CoV by RT-PCR, the fact that viral cultures were negative suggests that any virus present in stool might not have been infectious.

Even before diagnosis, but after his first healthcare encounter, the patient was concerned about having SARS after learning that other attendees of the Toronto religious retreat were infected. This concern led the patient and his household contacts to take precautions after the patient's onset of cough; these precautions included the intermittent use of surgical masks, which have been shown to be effective in reducing the risk for SARS-CoV infection (16). Routine cleaning and surface decontamination of the case-patient's household and hospital settings may have further reduced transmission. Finally, no medical procedures associated with increased risk for transmission, such as intubation or aerosolized nebulizer treatments, were performed on this patient (3). Taken in combination, low virus load in respiratory secretions, virus in stool that was potentially noninfectious, use of surgical masks by the case-patient and family, active infection control measures, and lack of aerosol-generating medical procedures may have all contributed to the lack of SARS-CoV transmission found in this investigation. Quantifying the impact that these and other factors have on the risk for transmission will require further epidemiologic evaluation around transmission events.

This investigation had some limitations. We chose a nonrandom sample of postdiagnosis contacts; however, since no SARS-CoV transmission to unprotected prediagnosis contacts was documented, the sampling scheme likely did not bias our findings toward lack of transmission. Furthermore, surveillance for fever and respiratory symptoms was ongoing in all contacts whether they participated in the investigation or not. We also cannot eliminate the possibility of some false-negative laboratory results, given that sensitivity of serologic assays and RT-PCR is lower early in illness (17,18,21). Nevertheless, Peiris et al. (21) showed that immunoglobulin (Ig) G isotype-specific antibody to SARS-CoV was detected in 93% of patients meeting a probable SARS case definition by day 28 after onset of symptoms, and the mean time to seroconversion was 20 days. Since serum samples were obtained for 22 of the prediagnosis contacts (85%) by day 20 and for 14 (54%) by at least day 28 after last exposure to the case-patient, that we missed seroconversions seems unlikely.

This patient was recognized as a probable SARS case-patient 2.5 hours after arrival in the emergency department, which was relatively rapid, given that neither WHO nor CDC had included Toronto as part of the interim SARS case definitions at the time of this patient's diagnosis. Toronto was subsequently added to the list of areas with suspected or documented community transmission in response to reports of SARS transmission among attendees at the gathering that led to this patient's infection (12,15). However, since very short exposure times have been associated with extensive SARS transmission elsewhere (16), vigilance is needed when caring for patients with recent exposure to a setting with an ongoing SARS outbreak,

even if local transmission has not been recognized. Draft guidelines are available to help identify future SARS case-patients (22), but since we do not know which patients with SARS will transmit readily, droplet and airborne infection control precautions should be implemented if a diagnosis of SARS is suspected.

Although this case-patient did not transmit SARS-CoV, many persons were symptomatic after contact with him, including two persons who met the suspected SARS case definition. To date, no asymptomatic SARS-CoV infection or transmission before onset of symptoms has been definitively documented. Until a diagnostic test is developed that is sensitive early in SARS-CoV infection, illness in a healthcare worker, household contact, or other close contact of a SARS case-patient remains the best existing criterion for requiring furlough or isolation of that person (23–25). However, due to the nonspecific clinical signs and symptoms of SARS (i.e., cough and fever), the clinical case definition has a low positive predictive value. This situation presents a challenge both for the management of close contacts of SARS patients and for surveillance for new SARS cases, particularly during the viral respiratory season, and emphasizes the need to identify an epidemiologic link as quickly as possible. Most (82%) symptomatic persons in this investigation had some degree of rhinorrhea, a symptom present in <25% of patients in descriptions of early clinical manifestations of SARS-CoV infection (5,6,26).

This type of epidemiologic investigation can be used in future investigations of transmission surrounding individual SARS case-patients; however, since such investigations are quite resource-intensive, this method would be most useful if applied to SARS case-patients linked to multiple transmission events, to assess risk factors associated with patients who readily transmit SARS-CoV. While factors contributing to SARS transmission are likely to be complex, additional data on the relationship between the natural history of infection and viral shedding, the types and duration of contacts with SARS patients, the effectiveness of infection control measures, and the contribution of each of these factors to transmission should help focus public health control measures to efficiently reduce SARS transmission.

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SARS-associated Coronavirus Transmission, United States

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To better assess the risk for transmission of the severe acute respiratory syndrome–associated coronavirus (SARS-CoV), we obtained serial specimens and clinical and exposure data from seven confirmed U.S. SARS patients and their 10 household contacts. SARS-CoV was detected in a day-14 sputum specimen from one case-patient and in five stool specimens from two case-patients. In one case-patient, SARS-CoV persisted in stool for at least 26 days after symptom onset. The highest amounts of virus were in the day-14 sputum sample and a day-14 stool sample. Residual respiratory symptoms were still present in recovered SARS case-patients 2 months after illness onset. Possible transmission of SARS-CoV occurred in one household contact, but this person had also traveled to a SARS-affected area. The data suggest that SARS-CoV is not always transmitted efficiently. Routine collection and testing of stool and sputum specimens of probable SARS case-patients may help the early detection of SARS-CoV infection.

Severe acute respiratory syndrome (SARS) was recently described as the clinical manifestation of infection by a novel coronavirus (CoV), the SARS-associated CoV (SARS-CoV) (1–5). This syndrome was first recognized in February 2003 in Vietnam, but it was later realized that the first cases occurred in southern China in November 2002 (6,7). Subsequently, the infection rapidly spread throughout the world, and by July 2003, when the World Health Organization declared that the outbreak was contained, 8,437 cases and 813 deaths in 32 countries had been reported (8).

As the outbreak developed, epidemiologic evidence suggested that SARS-CoV was transmitted by respiratory droplets or direct contact with infected patients and possibly by fomites (9–12). In certain circumstances, transmission of SARS-CoV was particularly efficient and resulted in individual patients infecting large numbers of people (referred to as "super-spreading events"), whereas in other situations, no secondary transmission was observed (13).

A better understanding of the duration of SARS-CoV shedding and virus quantities in respiratory secretions, stool, urine, and other body fluids and of the risk factors for spreading illness to close contacts is critical to accurately assess the risk for transmission and to develop effective control strategies. To that end, we obtained serial biologic specimens and clinical and exposure data for 5 to 10 weeks after onset of illness from seven laboratory-confirmed U.S. SARS patients and their household contacts.

Materials and Methods

Participants

We targeted 103 patients who met the Centers for Disease Control and Prevention's (CDC's) surveillance case definition for probable SARS (14). Of these patients, 7 (7%) with laboratory-confirmed SARS-CoV infection (antibodies to SARS-CoV were detected) were enrolled;

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19 (18%), including 1 confirmed SARS case-patient, declined participation; and 77 (75%) were excluded for various reasons (negative for SARS-CoV antibody at ≥21 days after illness onset, a confirmed alternative diagnosis, or foreign citizen not residing in the United States). The household contacts of seven laboratory-confirmed case-patients were also enrolled. Household contacts were defined as persons who had lived in the same household with SARS case-patients during their illness. All participants provided informed consent.

Timeline for Follow-up Visits

Follow-up visits were scheduled twice a week for the first 3 weeks after illness onset and then once a week for 2 weeks. If a case-patient was first enrolled after week 5 of illness, then a follow-up visit was made as soon as feasible after enrollment. Some case-patients were enrolled at >5 weeks after illness onset and, therefore, were followed up for >10 weeks. For household contacts, visits were scheduled once weekly for a period of 4 weeks after initial exposure to the case-patient. A single follow-up visit was scheduled if the household contact was enrolled >4 weeks after initial exposure to the case-patient.

Clinical and Epidemiologic Data

At the initial visit with the SARS case-patients, we collected data on demographics, date of illness onset, clinical symptoms, and exposure history. At the initial visit with household contacts, we gathered data on any illness they had had since their exposure to the case-patient and on the types and patterns of exposure (e.g., sleeping in the same room at night, daily contact within <3 feet, and direct skin-to-skin contact, such as kissing or hugging, with case-patients). At each subsequent visit, we collected information on any symptoms experienced by case-patients or household contacts since their previous visit, including symptoms during the current visit.

Clinical Specimens

Specimens collected as a part of the diagnostic work-up were available for this investigation, and at each postenrollment visit, participants were asked to provide whole-blood, serum, stool, urine, nasopharyngeal, and oropharyngeal swab specimens. We obtained 1–10 mL of blood from adults and 0.5–5 mL of blood from children <3 years old by venipuncture or finger stick. Clotted blood was centrifuged, and serum was separated before being shipped to CDC for testing. Similar volumes of whole blood were collected in a tube containing EDTA. Nasopharyngeal and oropharyngeal samples were collected by use of a single Dacron swab with a nonwooden shaft; the swab was then placed in a sterile vial containing 2 mL of viral transport medium. Stool specimens were collected in a sterile container and sealed. Participants provided a 50-mL clean-catch collection of urine in a sterile urine cup. Specimens were processed and stored according to CDC laboratory biosafety guidelines (15). All specimens were stored at 4°C for a maximum of 72 h and shipped on ice to the CDC laboratory. If shipping within 72 h was not feasible, specimens were stored at –70°C and then shipped.

Laboratory Methods

To detect SARS-CoV in stool, urine, and respiratory specimens, we performed reverse transcriptase–polymerase chain reaction (RT-PCR), using primers targeted to the polymerase and nucleocapsid genes of the SARS-CoV genome, as described elsewhere (2, Emery et al., unpub data). Stool samples were prepared as 10% extracts in Tris-HCl buffer before isolation of total nucleic acid for RT-PCR testing. To quantify the virus load in respiratory and stool specimens, quantitative RT-PCR was performed using the TaqMan assay and standard curves generated from synthetic RNA transcripts (S. S. Monroe and R. S. Beard, unpub. data). Previously described culture techniques (2) were used to isolate SARS-CoV from specimens. To determine the S and N gene sequences of SARS-CoV, a set of 10 overlapping RT-PCR products, which cover the entire open reading frames of the S (8 products) and N (2 products) genes, were generated by using the SuperScript One-Step RT-PCR with Platinum Taq (Invitrogen, Carlsbad, CA) and sequenced by using 16 (S gene) or 7 (N gene) sequencing primers (S. Tong et al, unpub. data). Serum specimens were tested for SARS-CoV–associated antibodies by use of an enzyme-linked immunosorbent assay and an indirect fluorescent antibody test, using previously described methods (2). Serum specimens were considered positive only if results for both tests were positive using predetermined cut-offs (2).

Results

Follow-up Findings

Five of seven enrolled case-patients provided data on residual symptoms. Three case-patients reported shortness of breath that persisted at least until days 50, 56, and 62, respectively, after onset of fever. Two case-patients reported residual coughing: case-patient 4 reported a dry cough until day 50 and case-patient 2 reported a productive cough until day 56 after onset of fever. These symptoms had been reported during the acute phase of each case-patient's illness. Wheezing developed in one case-patient without a previous history of respiratory disease at day 11 of illness and persisted at least until day 46. No data were available to characterize the progression of symptoms over time.

Of 41 respiratory specimens obtained from seven case-patients (Table 1), 4 (10%) were sputum samples from two

Table 1. Timing of collection of clinical specimens from seven confirmed SARS case-patients, United States, 2003

Specimen type	No. of specimens (no. of case-patients) by no. of days after illness onset			Total no. of specimens
	0–14 days	15–28 days	>28 days	
Respiratory	11 (7)	12 (4)	18 (7)	41
Sputum	2 (2)	2 (1)	0 (0)	4
NP swab	5 (5)	4 (4)	9 (6)	18
OP swab	2 (2)	6 (4)	9 (7)	17
Nasal aspirate	1 (1)	0 (0)	0 (0)	1
Nasal wash	1 (1)	0 (0)	0 (0)	1
Stool	1 (1)	5 (2)	8 (6)	14
Urine	0 (0)	2 (2)	6 (5)	8
Serum/blood	18 (7)	15 (4)	15 (7)	48

[a]SARS, severe acute respiratory syndrome; NP, nasopharyngeal; OP, oropharyngeal.

case-patients (1 from case-patient 5 and 3 from case-patient 7). SARS-CoV was detected by both RT-PCR and viral culture in the sputum sample of case-patient 5, which was collected at day 14 after illness onset (Figure). All other respiratory specimens, including seven nasopharyngeal and oropharyngeal swab samples collected during the first 2 weeks of illness from five case-patients, tested negative by RT-PCR.

A total of 14 stool specimens were obtained from seven case-patients: two patients provided 4 samples each, one patient had 2 samples, and four had 1 sample each. SARS-CoV RNA was detected in five specimens, all of which came from two case-patients (one specimen from case-patient 6 and four specimens from case-patient 7) (Figure). The single positive stool specimen from case-patient 6 was obtained 19 days after onset; his subsequent stool specimens (collected at days 23, 32, and 44) tested negative for SARS-CoV by RT-PCR. The first stool specimen from case-patient 7 was collected on day 14 of illness; viral RNA was detected in all four of his stools, including the last one, which was collected at day 26. SARS-CoV was not isolated by culture from any of the RT-PCR–positive stool specimens.

The highest concentrations of SARS-CoV were detected in sputum from case-patient 5 (43 million copies per gram of specimen) and in the day-14 stool from case-patient 7 (37 million copies per gram of specimen) (Table 2). After day 14 of illness, the concentration of virus in stool specimens from case-patient 7 dropped by 20-fold or more. Of note, this case-patient reported moderate diarrhea from days 2 to 12 of illness. Case-patient 6 had only mild diarrhea during the first 4 days of illness, and the amount of virus in his stool sample that was collected on day 19 (i.e., 2 weeks after the resolution of diarrhea) was approximately 800-fold lower than the amount in the day-14 stool sample of case-patient 7 and approximately 50-fold lower than that found in subsequent specimens from case-patient 7. No evidence was found that the virus mutated in case-patient 7 during the infection: genomic sequences of S and N genes of SARS-CoV from all positive stool specimens of this case-patient were identical.

No viral RNA was detected by RT-PCR in any of the eight urine specimens collected from the seven case-patients. SARS-CoV antibody was first found as early as days 10 and 11 after illness onset in three of seven case-patients. Adequate specimens were not available to characterize the time of first detectable SARS-CoV antibody in the remaining four case-patients (Table 3).

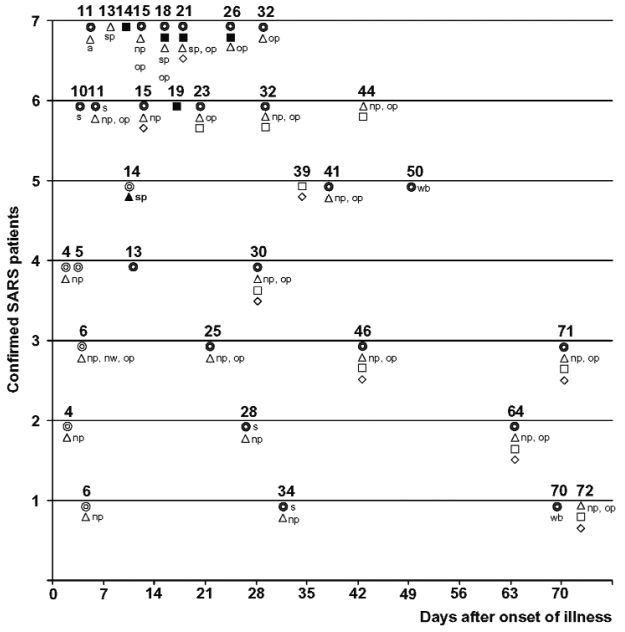

Figure. Detecting severe acute respiratory syndrome-associated coronavirus (SARS-CoV) RNA by reverse transcriptase-polymerase chain reaction (RT-PCR) and SARS-CoV antibodies by enzyme-linked immunosorbent assay (ELISA) in clinical specimens from seven confirmed SARS case-patients, United States, 2003. Circle within circle: blood specimens (same symbol represents both whole blood and serum when both specimens are collected and results are entirely concordant. s, serum; wb, whole blood (symbols are labeled s or wb if either blood or serum was collected). Blocked symbols denote SARS-CoV-positive specimens by ELISA. △ : respiratory specimens (include np, nasopharyngeal swab; nw, nasal wash; a, nasal aspirate; op, oropharyngeal swab; sp, sputum). □ : stool. ◇ : urine. Blocked symbols denote SARS-CoV-positive specimens by RT-PCR.

Table 2. Quantities of SARS-CoV in sputum and stool specimens from three confirmed SARS case-patients, as measured by quantitative RT-PCR, United States, 2003[a]

Case-patient identification no.	Specimen	Time of specimen collection after illness onset (no. of days)	Copies per gram of sample
5	Sputum	14	43,000,000
7	Stool	14	37,000,000
	Stool	18	1,600,000
	Stool	21	930,000
	Stool	26	2,300,000
6	Stool	19	45,000

[a]SARS-CoV, severe acute respiratory syndrome–associated coronavirus; RT-PCR, reverse transcriptase–polymerase chain reaction.

Household Transmission

Ten household contacts of five of the seven SARS case-patients were enrolled. Case-patient 1 had four household contacts, case-patients 3 and 4 had one such contact each, and case-patients 6 and 7 had two household contacts each. Of the 10 household contacts, 4 were female, 2 were smokers, and 2 reported previous history of respiratory problems (sarcoidosis in household contact 5 and pulmonary embolus in household contact 7).

Household contact 1 (who was also case-patient 2) was the only such contact who tested positive for SARS-CoV antibody. The remaining nine household contacts were negative for SARS-CoV antibody in specimens collected ≥28 days after their initial exposure to a case-patient. The infected household contact was the wife of confirmed SARS case-patient 1. The couple had visited Hong Kong together in early March 2003 and stayed at Hotel M, which was subsequently linked to the initial spread of SARS (16), where they had multiple opportunities for exposure. Case-patient 1 became ill 7 days after returning to the United States from Hong Kong. Symptoms developed in household contact 1 some 13 days after returning to the United States and 6 days after onset of illness in her husband. SARS-like symptoms did not develop in any of the three other household contacts of case-patient 1, nor did any have laboratory evidence of SARS-CoV infection. The analysis of household exposures and protective measures in this household indicated that household contact 1 had more frequent unprotected contact with the index patient compared with three other household contacts (Table 4).

The remaining six uninfected household contacts reported close contact (e.g., contact within 3 feet and unprotected skin-to-skin contact) with case-patients. The exposure of four household contacts of two case-patients with stool specimens positive for SARS-CoV was limited by isolation of the case-patients in a separate room with a private bathroom during the first week of illness. Both case-patients also wore surgical masks during this period, as did three of their four household contacts. Case-patient 7 was hospitalized from day 11 to day 18 of illness, the period during which the highest amounts of virus were detected in his stool, and continued to be positive for SARS-CoV in stool after discharge. Neither case-patient 7 nor his two household contacts wore surgical masks after being discharged from the hospital. Case-patient 6, who was never hospitalized, had low-level shedding of SARS-CoV in stool on day 19, but no virus was subsequently found in his stool specimens. One of his two household contacts wore a mask until 10 days after the resolution of fever in the case-patient.

Discussion

In this investigation of U.S. SARS-CoV–infected persons and their household contacts, we identified probable transmission of SARS-CoV to only 1 of 10 such contacts.

Table 3. SARS-CoV antibodies as determined by enzyme-linked immunosorbent assay in seven confirmed SARS case-patients, by number of days after illness onset, United States, 2003[a]

Case-patient	Days after illness onset	SARS-CoV antibodies[b]
Patient 1	6	Negative
	34	1,600
Patient 2	4	Negative
	28	6,400
	64	6,400
Patient 3	6	Negative
	25	6,400
	46	1,600
	71	1,600
Patient 4	2	Negative
	5	Negative
	13	Negative
	30	6,400
Patient 5	14	Negative
	41	1,600
Patient 6	10	1,600
	11	1,600
	15	6,400
	23	6,400
Patient 7	11	400
	15	1,600
	18	6,400
	21	6,400
	26	1,600
	32	6,400

[a]SARS-CoV, severe acute respiratory syndrome–associated coronavirus.
[b]Reciprocal of dilution.

Table 4. Profile and exposure of 10 household contacts (HHCs) of five confirmed SARS case-patients, United States, 2003

							Exposure to the case-patient before hospitalization				Protective measures by HHC	
HHC no.	Case-patient identification no. (n=5)	Shedding documented in case-patient	Use of surgical mask by case-patient	SARS-CoV infection in HHC	HHC relation to case-patient	Age (y)/sex/ race	No. of days in house with case-patient	No. of nights in same room	Contact within 3 feet (h/day)	Skin-to-skin contact (times/day)	Surgical mask used during 1st week of illness	Routine handwashing with soap
1[b]	1	No	No	Yes	Spouse	37/F/A	4	5–6	0–1	>3	No	No[c]
2				No	Brother	57/M/A	4	0	1–3	0	No	No[c]
3				No	Brother-in-law	55/M/A	4	0	0–1	0	No	Yes
4				No	Nephew	16/M/A	4	0	0–1	0	No	Yes
5	3	No	No	No	Spouse	52/M/W	6	7	>7	>3	No	Yes
6	4	No	No	No	Mother	52/F/W	4	0	>7	>3	No	Yes
7	6[d]	Yes	Yes	No	Spouse	47/F/W	All[e]	0	0–1	1–2	Yes	Yes
8				No	Son	12/M/W	All[e]	0	1–3	1–2	No	Yes
9	7[f]	Yes	Yes	No	Son	22/M/A	11	0	0–1	1–2	Yes	Yes
10				No	Daughter	15/F/A	11	0	0–1	0	Yes	Yes

[a]SARS, severe acute respiratory syndrome; F, female; M, male; A, Asian; W, white.
[b]SARS coronavirus antibody–positive HHC.
[c]No soap used for handwashing (water only).
[d]Shedding documented in stool on day 19 after onset of illness.
[e]Case-patient 6 was never hospitalized.
[f]Shedding documented in stool on days 14, 18, 21, and 26 after onset of illness.

We detected SARS-CoV in fecal and respiratory specimens and found that SARS case-patients may have high concentrations of virus in stools during the 2nd week of illness and continue to shed the virus in feces until at least 26 days after onset of symptoms. The amount of SARS-CoV in stool from a case-patient with moderate diarrhea was similarly high to the quantity seen in a sputum specimen collected from a different case-patient at the same interval after illness onset. However, no virus could be cultured from any stool specimens that were PCR-positive for SARS-CoV, suggesting that SARS-CoV in feces may be present in the form of either nonviable viral particles or antibody-coated virus.

The one household contact who became infected was the person who had more contact with the potential source case-patient during the first week of illness than did other members in the household. This contact was also exposed in Hong Kong along with her husband; however, she became ill >10 days after returning to the United States (16). Previously reported data suggest that the incubation period for SARS ranges from 2 to 10 days (4,17), but in some cases, the incubation period may be as long as 14 days (18). Therefore, the possibility remains that this contact may have been infected in Hong Kong. The remaining uninfected household contacts included four contacts of two case-patients with positive stool specimens in whose households simple infection-control procedures were implemented during the acute phase of illness in the index patient.

The lack of widespread household transmission of SARS found in our investigation is similar to findings in reports of the outbreak in Toronto, where 2 (6%) of 33 household contacts were infected despite unprotected contact with a SARS case-patient (19), and from the Philippines, where <1% of nonhospital contacts were reported to be infected (20). This finding supports the idea that in certain circumstances, SARS-CoV is not easily transmitted. Transmission may also be more likely to occur at the time when patients are shedding higher amounts of virus, and this period may coincide with their hospitalization, thus decreasing the degree of exposure for household contacts.

We were unable to detect SARS-CoV in specimens of our case-patients before day 14 after illness onset. We only detected virus in three case-patients: in a sputum sample of one patient at day 14 and in stool samples of two patients at day ≥14. All upper respiratory specimens in the first 2 weeks after onset were negative for SARS-CoV by RT-PCR; this finding differs from a report in Hong Kong, where viral RNA was detected in nasopharyngeal aspirates of 68% of case-patients at day 14 (21). Our inability to detect the virus in early respiratory samples may be associated with the type (nasopharyngeal and oropharyngeal swabs versus nasopharyngeal aspirates) of collected specimens, as well as with low amounts of virus generally seen in such specimens (1). Sputum samples may have a higher concentration of virus than upper respiratory specimens (1), consistent with our findings. Stool specimens have been found positive more frequently than upper respiratory specimens during the 2nd and 3rd week of illness, which is in accord with the limited results of this study. The inability to detect SARS-CoV in urine may be the result of a late collection of urine specimens (>14 days after illness onset). A wider use of steroids in treatment of

case-patients in Hong Kong compared with case-patients in the United States may have also altered the pattern of shedding of SARS-CoV.

Persistent respiratory symptoms that were reported up until at least 2 months after onset by most of our case-patients were similar to symptoms observed by Avendano et al. (19) in a study of Canadian healthcare workers who were followed for 5 weeks after illness onset, suggesting residual illness in SARS case-patients. However, the progression of these symptoms over time is difficult to interpret without a better appreciation of the pre-illness symptoms. Antibody to SARS-CoV in some case-patients was documented as early as day 10 after illness onset. We did not have an adequate number of early serum specimens from other case-patients to determine when SARS-CoV antibody is first detectable.

Results of this investigation should be interpreted in light of several limitations. The small number of participants does not allow for accurate estimation of the risk for transmission to household members. Irregular and long intervals between collections of specimens do not permit a clear picture of the natural history of SARS-CoV infection, including documenting the precise timing of the first appearance of SARS-CoV antibody. We also may have missed the presence of shedding in stools of other case-patients who had reported diarrhea during the acute phase of illness. Possible variations in specimen collection and handling techniques could also have affected SARS-CoV detection rates in respiratory and stool specimens.

Our results suggest that SARS-CoV is not always transmitted efficiently. Routine collection and testing of stool and sputum specimens of probable SARS case-patients may help the early detection of SARS-CoV infection. A follow-up of recovered SARS case-patients over several months would also help to better assess possible waning of antibody titers and long-term sequelae of the disease and, thus, improve our understanding of the true illness associated with SARS-CoV infection.

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Secondary Household Transmission of SARS, Singapore

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Secondary household transmission of severe acute respiratory syndrome (SARS) was studied in 114 households involving 417 contacts. The attack rate was low (6.2%). Occupation of the index case was the factor that most influenced household transmission (adjusted hazard ratio for healthcare workers 0.157; 95% confidence interval 0.042 to 0.588).

Severe acute respiratory syndrome (SARS) is an emerging infectious disease caused by the SARS-associated coronavirus (SARS-CoV) (1). Attack rates are >50% in hospitals (2). A similar trend was seen in Singapore, with SARS spreading to five hospitals and two Specialty Centres within 8 weeks (3). This rapid rate of transmission caused a national health alert and resulted in large amounts of manpower and resources being deployed.

On the other hand, transmission within the household was less efficient. We, therefore, examined the attack rate and the factors influencing secondary transmission of SARS in Singapore households. Data on probable SARS cases were collected by Singapore's Ministry of Health Epidemiology Unit, Singapore. The case definition of probable SARS was in accordance with the World Health Organization (WHO) (4).

Probable SARS cases that were also a household index were identified by using the definition that follow. A household was defined as a residential place with a unique address. A household index was a person with probable SARS and the first person to introduce SARS into the household. A household contact was defined as a person living in the same household as the household index.

Demographic and clinical data were collected. For the household index, the following information was collected: age, sex, if the household index was a healthcare worker (defined as a person who works in a healthcare setting), number of days spent at home after onset of symptoms, and number of contacts in household. For household contacts, the following information was collected: age, sex, if the contact was a healthcare worker, and if the contact was a family member. The week of the SARS outbreak in Singapore was also evaluated to see if there was a time trend in the risk for transmission.

All household contacts were followed prospectively for (1) clinical symptoms until 20 days after the last contact with the household index, and (2) evidence of positive PCR (polymerase chain reaction) or serologic test for SARS-CoV (according to criteria set by WHO). Secondary household transmission was said to have occurred if the household contact fulfilled the case definition of probable SARS (4).

Households were excluded if the household index lived alone, the household index did not spend time at home after onset of symptoms, if the period of household exposure to the index was not clearly defined (e.g., not isolated promptly upon hospital admission), or more than one index lived in the household (shown through contact tracing or onset <2 days after SARS developed in the first person in the household).

Statistical tests (Mann-Whitney, chi-square and Fisher exact test) were used to test for associations when appropriate. The Cox regression model was used to evaluate the influence of demographic and clinical factors on secondary household transmission. All analyses were performed with SPSS version 11.5.

There were 205 probable SARS cases in Singapore during the period between February 24 and April 29, 2003. These 205 probable SARS cases resided in 163 households. A total of 114 households fulfilled the inclusion and exclusion criteria. Forty-nine households were excluded (12 because the index lived alone, 20 because the household index did not spend time at home after onset of symptoms, 10 because the period of household exposure to the index was not clearly defined, 7 because more than one index patient was in that household). Seventy-two of the 114 household indexes (63.2%) were healthcare workers.

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Ten were doctors, 37 were nurses, 4 were nursing students, and 21 were paramedical staff.

From these 114 households, 417 household contacts were identified and followed prospectively. Secondary transmission occurred in only 14 households (12.3%), giving rise to 26 household cases of probable SARS. Household transmissions occurred within 2–11 days (mean 5.3 ± 2.6 days) after the onset of symptoms in the index cases. Symptoms developed in eight contacts (30%) while on home quarantine orders. The remaining 18 were not given home quarantine orders because they were either already in hospital with SARS or were not identified by contact tracing. The mean length of stay at home after onset of symptoms was not statistically different between the home-quarantined group and the group not quarantined at home ($p = 0.09$).

The secondary household attack rate was thus low (6.2% [95% confidence interval 3.9% to 8.6%]) and concurs with that reported by Beijing, China (5). In that study, the attack rate was 4.6% in persons who had contact with a probable SARS case-patient during the symptomatic period and lived in the same residence (which included some persons who visited or cared for a SARS patient). These findings are in contrast to the high attack rate seen in the healthcare setting (6). One possible explanation for this difference is the phase of the illness. SARS case-patients in the household tend to be in the early phase of illness whereas SARS case-patients in the healthcare settings tend to be in the later phase. In addition, coexisting conditions and invasive procedures done within the hospital setting may also influence risk of transmitting disease (7).

The low rate of household transmission suggests that the magnitude of a household outbreak would be less than a hospital-based one, which could help allay public fear and panic, a societal concern evident in the recent outbreak (2,7). This knowledge will also enable public health officers to develop a more sensitive and responsive surveillance system. As the expected attack rate is known, healthcare professionals can be prepared early if the observed attack rate in the households is higher than predicted, allowing rational rather than empirical implementation of public health measures and justify rapid and aggressive investigative and containment measures needed to prevent a large outbreak. These considerations are particularly important for countries with limited healthcare and fiscal resources. In Singapore, we learned the usefulness of educating persons on the need and means of doing daily temperature monitoring, to have a centralized temperature recording database for hospital staff and patients so that a cluster of fevers could be spotted early, to evaluate symptomatic hospital staff in designated hospital clinics, and to trace contacts by using many resources including the police and army. The authorities in Hong Kong did not have the benefit of this information as little was known then about SARS. Perhaps in the future, such knowledge will help prevent another situation similar to that seen in Amoy Gardens, Hong Kong Special Administrative Region (8).

Factors influencing household transmission were also studied in the Singapore cohort. Univariate analysis (Table 1) showed that household index cases were less likely to transmit SARS to their household contacts if they were younger or were healthcare workers. Contacts were more likely to develop SARS if they were family members or nonhealthcare workers. The Cox regression model (Figure and Table 2) verified two of these four factors, index occupation and age.

The most consistent and important factor influencing household transmission was whether or not the index case was a healthcare worker (adjusted hazard ratio 0.157; 95% CI 0.042 to 0.588). This was independent of length of exposure or demographics. The reason for this finding was not evident from the data available. A difference in social behavior between healthcare worker and nonhealthcare worker is a possible explanation for this disparity in risks of household transmission. For example, healthcare work-

Table 1. Characteristics of household contacts and index cases[a]

Risk Factor	Household contacts with SARS (n = 26) (mean ± 1 SD)	Household contacts without SARS (n = 391) (mean ± 1 SD)	p value
Household contact			
Age (y)	35.3 ± 19.8	30.3 ± 17.4	0.17
Sex (female)	14 (53.8%)	225 (57.5%)	0.71
Healthcare worker	1 (3.8%)	84 (21.5%)	0.04
Family member	24 (92.3%)	269 (68.8%)	0.01
Index case			
Age (y)	53.5 ± 16.2	35.4 ± 13.6	<0.001
Sex (female)	20 (76.9%)	290 (74.2%)	0.76
Healthcare worker	4 (15.4%)	273 (69.8%)	<0.001
Days index spent at home after onset of symptoms	5.3 ± 2.5	4.8 ± 2.5	0.43
No. of persons in household	5.0 ± 3.0	4.8 ± 2.4	0.79

[a]Using univariate analysis, SARS, severe acute respiratory syndrome.

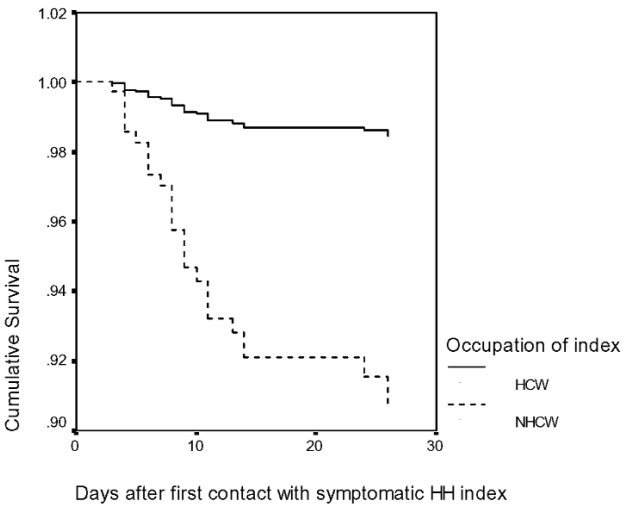

Figure. Survival analysis for secondary household transmission (Cox regression model). Household contacts were more likely to get SARS if the index was older or a nonhealthcare worker. Hazard ratios of risk factors analyzed are tabulated in Table 2. The -2log likelihood for this analysis was 253.77. HH, household; HCW, healthcare worker; NHCW, nonhealthcare worker.

ers may be more acutely aware of the risk of acquiring and transmitting SARS and may alter hygiene practices at home. In addition, better health and disease prevention knowledge may influence the efficacy of such practices. Qualitative differences in social behavior between healthcare worker and nonhealthcare worker should be investigated, as this knowledge may be useful in containing future SARS outbreaks.

Table 2. Hazard ratios of risk factors analyzed[a]

Independent risk factor	Hazard ratio (95% CI)	p value
Household contact		
Age (yrs)	1.013 (0.992 to 1.034)	0.222
Sex (female)	1.232 (0.542 to 2.796)	0.619
Healthcare worker	1.692 (0.137 to 20.926)	0.682
Family member	1.936 (0.372 to 10.076)	0.432
Household index		
Age (y)	1.055 (1.015 to 1.097)	0.007
Sex (female)	1.274 (0.451 to 3.595)	0.648
Healthcare worker	0.157 (0.042 to 0.588)	0.006
Days index spent at home after onset of symptoms	0.942 (0.794 to 1.117)	0.493
No. of persons in household	1.060 (0.899 to 1.249)	0.490
Week of outbreak	1.019 (0.733 to 1.417)	0.911

[a] Using Cox Regression Model; CI, confidence interval.

The risk for household transmission was also lower if the index case was younger. This finding may correlate with milder disease seen in younger persons and lower infectivity. The week of the outbreak did not significantly influence the model, indicating the lack of a time trend in household transmission.

In conclusion, this study is the first to characterize secondary household transmission of SARS. We have shown that the attack rate is low and the most significant factor influencing household transmission was the occupation of the index case. The results of this study challenge some of the current concepts about SARS. Given that the study numbers are not large, a multicenter analysis of the past SARS cases would be helpful in verifying these findings.

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Dr. Denise Goh is a pediatrician and geneticist at the National University of Singapore and the National University Hospital, Singapore. Her interests are in childhood diseases.

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Probable Secondary Infections in Households of SARS Patients in Hong Kong

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Although severe acute respiratory syndrome (SARS) is highly infectious in clinical settings, SARS has not been well examined in household settings. The household and household member attack rates were calculated for 1,214 SARS case-patients and their household members, stratified by two phases of the epidemic. A case-control analysis identified risk factors for secondary infection. Secondary infection occurred in 14.9% (22.1% versus 11% in earlier and later phases) of all households and 8% (11.7% versus 5.9% in the earlier and later phases) of all household members. Healthcare workers' households were less likely to be affected. Risk factors from the multivariate analysis included at-home duration before hospitalization, hospital visitation to the SARS patient (and mask use during the visit), and frequency of close contact. SARS transmission at the household level was not negligible in Hong Kong. Transmission rates may be greatly reduced with precautionary measures taken by household members of SARS patients.

The first large-scale severe acute respiratory syndrome (SARS) outbreak occurred in the Prince of Wales Hospital in Hong Kong on approximately March 11, 2003 (1,2). It was followed by a large-scale community outbreak in the Amoy Gardens Estate, which had a total of 321 SARS cases as of April 15, 2003; 41.0% were in Block E residents (3) . Environmental transmission of SARS was most likely primarily responsible for the Amoy Gardens outbreak (4,5) . As of May 31, 2003, a total of 1,739 suspected or confirmed SARS cases were reported in Hong Kong, of which 384 were in hospital workers (22.1%) and approximately 321 were in residents of the Amoy Gardens (6) (Figure).

In the clinical setting, a very high attack rate of the SARS virus has been observed (7,8). However, few data describe the attack rates in community settings. The first objective of the study is to estimate the household attack rates and the household member attack rates for different categories of SARS patients. The second objective is to investigate risk factors associated with these two attack rates.

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Methods

Study Population

The study population comprised all SARS case-patients who were reported to the Department of Health on or before May 16, 2003 (n = 1,690), and their household members (including kin, nonkin, and domestic helpers). In Hong Kong, confirmed or suspected SARS patients were defined as those with radiographic evidence of infiltrates consistent with pneumonia, and fever >38°C degrees any time in the preceding 2 days, and at least two of the following symptoms: 1) history of chills in the past 2 days, 2) cough or breathing difficulty, 3) general malaise or myalgia, or 4) known history of exposure (9). This definition is the same as that of the World Health Organization for probable cases (8).

In this study, an index patient is defined as the SARS case-patient who had the earliest date of fever onset within a household. Household members who had an onset of symptoms later than the index patient are considered to be probable secondary (or tertiary) cases. Three of these cases were hospital workers who may have contracted SARS in the hospital setting and were hence excluded from the analysis.

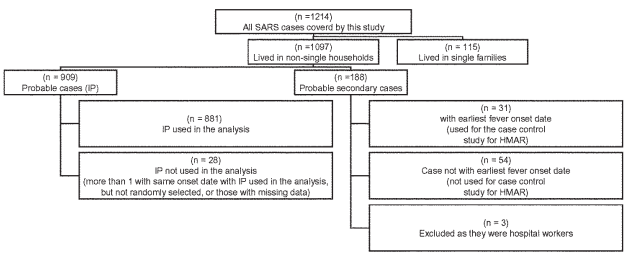

Figure. Distribution of the SARS patients covered in this study.

Data Collection

The list of telephone numbers, as well as some demographic and clinical background information of all probable SARS cases in Hong Kong (identified on or before May 16, 2003 [n = 1,690]), were obtained from the Department of Health. A team of trained interviewers called these numbers and briefed the person answering the telephone about the nature of the study. The interviewer then identified the person who had the earliest date of fever onset and confirmed that the household members had not been interviewed twice. When a household had two or more SARS cases with the same fever onset date (11 households), one of them was randomly selected as the index patient. Respondents were then requested to hand the telephone to the household member (who may or may not be the index patient) who was most familiar with the household situation to serve as the responder. The interview occurred at least 14 days after the index patient's onset of symptoms past the maximum incubation period of 10 days.

By using a SARS registry, a research staff member later crosschecked that the index patient named by the interviewee was, in fact, the one with the earliest onset of fever, if there were more than one SARS case-patient in the household. In July, the names of all family members provided by the respondents were also checked against the registry to ensure that the study had not missed any probable secondary cases. This check also ensured that no duplicate interviews had been conducted.

The study was conducted from April 4, 2003, to June 10, 2003. Of the 1,690 probable SARS cases reported in Hong Kong as of May 16, a total of 1,214 (72%) SARS cases had been covered by the study (Figure). The 1,214 SARS cases came from 996 households (881 households were analyzed and 115 single households were excluded from the analysis). Of the remaining 476 reported SARS cases in Hong Kong that were not covered by this study, 140 case households (8.2%) did not have a correct telephone number, 163 (9.6%) could not be contacted after at least 5 different attempts, 163 (9.6%) refused to participate in the study, and 10 (0.6%) were not in Hong Kong or could not communicate in Chinese or English.

Questionnaire

The study questionnaire collected the following information: 1) Sociodemographic data about the index patient and whether he or she resides in the Amoy Gardens (and apartment block number), 2) Household information—including all household members' names, ages, gender, and relationship with the index patient, and if they were hospital workers, 3) Information about any "probable secondary SARS infection" among household members, 4) Data regarding individual household members' hospital visits to the index patient, and 5) Data regarding close contact between individual household members and the index patient (Table 1).

Study Design

The household attack rate was defined as the number of households with at least one probable secondary SARS case divided by the total number of index patient's households. The household member attack rate was defined as the total number of all probable secondary or tertiary SARS case-patients of all relevant index patient's households divided by the total number of household members (not including the index patient) of all relevant index patient's households.

Two analyses were performed to identify risk factors associated with household attack rates and household member attack rates. Households that had at least one probable secondary infection were first compared with those households which had no probable secondary infections in a number of risk or protective factors. To control for any period effects, a dummy variable was created to represent the two time periods (before March 25, 2003, and on or after March 25, 2003). March 25 corresponds to the beginning of the Amoy Gardens outbreak; after that date, public awareness of SARS was greatly heightened (10). The average number of secondary cases from one SARS-infected person declined greatly from 2.7 in the initial part of the epidemic to 0.9 after March 25 (11). (These figures were derived from modeling methods [instead of a survey] and were not confined to household cases; hence, they are not comparable to the results obtained by this study).

The second analysis used a case-control design that compared individual family members who were probable secondary SARS case-patients with those who were not. To avoid ambiguities arising from distinguishing secondary and tertiary infections, only the "first" probable secondary cases were used as a case in this case-control analysis, if there were multiple SARS cases in the household. In addition, this analysis also examined the frequency of close contacts between the case or control and the index patient (e.g., dining together, sharing a bedroom).

Statistical Analyses

The household attack rates and the household member attack rates were calculated separately for four groups of index patients (hospital workers, Amoy Block E residents, other block residents, and other community members), and 95% confidence intervals (CI) were also derived. Univariate odds ratios and p values from chi-square test were obtained. Stepwise multivariate logistic regression methods using candidate variables that were, at a minimum, marginally significant in the univariate analysis ($p < 0.10$)

Table 1. Univariate association between various risk factors and Household Member Attack Rates (HMAR)

Risk factor	% attack rate: Case (n = 131)	% attack rate: Control (n = 2,139)	Odds ratio (95% CI)	Chi-square p value
Sex[a]				
Male	46.6	48.3	1.00	0.701
Female	53.4	51.7	1.07 (0.75 to 1.53)	
Age (y)[b]				
18–30	46.6	46.9	1.00	0.287
31–40	15.3	15.3	1.17 (0.68 to 2.01)	
41–50	16.2	16.3	1.04 (0.60 to 1.81)	
51–60	10.9	10.7	1.58 (0.90 to 2.76)	
≥61	11.1	10.8	1.65 (0.95 to 2.86)	
Type of Index Person (IP)				
Hospital workers	7.6	33.5	1.00	<0.001[c]
Amoy Gardens Block E residents	10.7	2.8	16.99 (7.23 to 39.90)	
Amoy Gardens other Block residents	15.3	10.6	6.31 (2.91 to 13.67)	
Other community members	66.4	53.2	5.48 (2.83 to 10.61)	
Date of IP's fever onset[d]				
Before March 25	51.9	34.2	1.00	<0.001
On or after March 25	48.1	65.8	0.48 (0.34 to 0.69)	
Duration IP stayed home between fever onset and hospitalization (d)[e]				
≤2	31.3	51.0	1.00	<0.001
3–5	32.1	30.3	1.72 (1.11 to 2.68)	
≥6	36.6	18.8	3.18 (2.07 to 4.90)	
IP visited by a family member during hospitalization?				
No	73.3	87.9	1.00	<0.001
Yes	26.7	12.1	2.65 (1.76 to 3.98)	
Mask use during hospital visits by a household member[f]				
Not visited by any household member	75.0	88.6	1.00	<0.001[c]
Visited, both with mask on	6.3	4.0	1.87 (0.88 to 3.96)	
Visited, one with mask on	5.5	3.6	1.78 (0.80 to 3.96)	
Visited, both without mask on	13.3	3.8	4.16 (2.37 to 7.30)	
Whether caretaker of IP				
No	64.9	82.0	1.00	<0.001
Yes	35.1	18.0	2.47 (1.70 to 3.60)	
Whether shared room or bed with IP[g]				
Never	59.7	81.3	1.00	<0.001
Sharing room	8.9	7.3	1.66 (0.86 to 3.19)	
Sharing room and bed	31.5	11.4	3.74 (2.48 to 5.64)	
Frequency of dining together with IP[h]				
Never	37.0	60.2	1.00	<0.001
<5	21.8	18.7	1.90 (1.15 to 3.12)	
5–10	14.3	9.7	2.40 (1.35 to 4.29)	
>10	26.9	11.4	3.82 (2.38 to 6.15)	
Frequency of close contact with IP (within 1 m)[i]				
Never	22.5	48.4	1.00	<0.001
Seldom	15.0	14.7	2.19 (1.19 to 4.02)	
Occasionally	24.2	16.4	3.17 (1.85 to 5.42)	
Frequent	38.3	20.5	4.03 (2.47 to 6.56)	
Frequency coughed at by IP (within 1 meter) [j]				
Never	77.6	90.3	1.00	<0.001[3]
Seldom	6.5	4.2	1.81 (0.81 to 4.03)	
Occasionally	10.3	2.8	4.29 (2.17 to 8.48)	
Frequent	5.6	2.6	2.47 (1.03 to 5.90)	

[a]Information on 31 controls missing.
[b]Information on 7 cases and 160 controls missing.
[c]Chi-square test exact p value.
[d]Information on 3 controls missing.
[e]Information on 6 controls missing.
[f]Information on 3 cases 18 controls missing.
[g]Information on 7 cases and 24 controls missing.
[h]Information on 12 cases and 51 controls missing.
[i]Information on 13 cases and 37 controls missing.
[j]Information on 24 cases and 98 controls missing.

were conducted to obtain factors independently associated with household attack rates and household member attack rates. Statistical Package for the Social Sciences (SPSS), Chicago, IL, Version 11 was used for all analyses.

Results

Background Characteristics of Index Patients

Of the respondents, 54.6% were female and 45.4% were male; most index patients were 18 to 50 years of age. Healthcare workers represented almost one third of the index patients and approximately 16% were Amoy Gardens Estate residents. Two-thirds of the index patients had fever onset during the later phase of the epidemic (on or after March 25), and most reported hospitalization within 5 days of fever onset (80.6%) and no hospital visits by household members (77.4%) (Table 2).

Table 2. Background characteristics of the Index Patient (IP)

Characteristic	n	%
Sex		
Male	400	45.4
Female	481	54.6
Age (y)[a]		
<18	44	5.1
18–30	239	27.8
31–40	197	22.9
41–50	165	19.2
51–60	76	8.8
≥61	138	16.1
Education level[b]		
No education	60	7.1
Primary	152	17.9
1-F3	123	14.5
F4-F5	208	24.5
F6-F7	44	5.2
University or above	263	31.0
Type of IP		
Hospital worker	267	30.3
Amoy Gardens Block E residents	36	4.1
Amoy Gardens other Block residents	107	12.1
Other community member	471	53.5
Duration IP stayed home between fever onset and hospitalization (d)[c]		
≤2	440	50.1
3–5	268	30.5
≥6	171	19.5
IP visited by any household member during hospitalization		
No	682	77.4
Yes	199	22.6
Date of IP's fever onset[d]		
Before March 25	299	34.0
On or after March 25	581	66.0

[a]22 missing persons.
[b]31 missing persons.
[c]2 missing persons.
[d]1 missing person.

Household Attack Rates

The overall household attack rate, as defined, was 14.9% (95% CI=12.6% to 17.4%) for all the households of the 881 index patients studied. Excluding households related to the Amoy Gardens, the household attack rate was 13.9% (96/738). The household attack rate was much higher for households of those index patients whose onset of fever occurred before March 25, 2003, than for those with onset of fever occurred on or after that date (22.4% versus 11.0%, OR = 0.43, p = 0.001). The Amoy Block E households had the highest household attack rate (38.9%), followed by those living in the other blocks of the Amoy Gardens (19.6%) and households of the "other community member" group (18.3%). The households with index patients who were healthcare workers had the lowest household attack rate (3.8%). Moreover, the household attack rates were higher for the earlier onset group as compared to the later onset group for all the four strata (Table 3).

Household Member Attack Rates

Among all 2,139 household members of the 881 index patients, a total of 188 (8%, 95% CI 7.0% to 9.2%) were probable secondary cases. The household member attack rates for the hospital healthcare worker group, the other community group, the Amoy non-Block E group, and the Amoy Block E group were 1.9%, 9.8%, 11%, and 24.4%, respectively. Excluding households related to Amoy Gardens, the household member attack rate was 6.9% (138/1,991). Similar period effects were observed: the odds ratios for comparing the two fever onset groups (on or after versus before March 25, 2003) were 0.15 (hospital healthcare worker group p = 0.004), 0.41 (other community group, p < 0.001), and 0.29 (Amoy non-Block E group, p = 0.002). For Amoy Block E respondents, the figures for the earlier and later onset groups were 37.1% and 17.7%, respectively (p = 0.058) (Table 3). The median duration between the date of onset of the index patients' symptoms and their "first" probable secondary case was 6.5, 7.0, 2.0, and 4.0 days for the healthcare worker, other community members, Amoy Block E, and Amoy non-Block E groups, respectively.

Factors Associated with Household Attack Rates

While sex of the index patient was not a significant factor, older age of index patient (OR = 1.57–3.77), type of index patient (OR = 5.74–16.35), longer duration home stay between fever onset and hospitalization (OR = 1.76–3.91), whether any household members visited the index patient (OR = 2.03), date of onset fever of index patient (later versus earlier onset groups, OR = 0.43) were all univariately associated with household attack rates (Table 4). Disinfection of the living quarter after the index patient's onset of fever was, however, not a significant

Table 3. Household attack rates (HAR) and household member attack rates (HMAR) for different categories of index patient

Type of index patient	% attack rate, Date IP's fever onset <March 25, 2003	% attack rate, Date IP's fever onset ≥March 25, 2003	Overall	Odds ratio (95% CI)[a]	chi-square p value
HAR					
Hospital workers	n = 114	n = 153	n = 267		
	7.0 (3.1–13.4)	1.3 (0.2–4.6)	3.8 (1.8–6.8)	0.18 (0.02 to 0.91)[b]	0.021
Other community members	n=148	n = 322	n = 471		
	29.1 (21.9–37.1)	13.4 (9.8–17.6)	18.3 (14.9–22.1)	0.38 (0.23 to 0.62)	<0.001
Amoy Gardens Block E residents	n = 12	n = 24	n = 36		
	50.0 (21.1– 78.9)	33.3 (15.6–55.3)	38.9 (23.1–56.5)	0.50 (0.10, to 2.54)	0.441[c]
Amoy Gardens other Block residents	n = 25	n = 82	n = 107		
	40.0 (21.1–61.3)	13.4 (6.9–22.7)	19.6 (12.6–28.4)	0.23 (0.07, 0.72)	0.008[c]
All households of all IP	n = 299	n = 581	n = 881		
	22.4 (17.8–27.6)	11.0 (8.6–13.9)	14.9 (12.6–17.4)	0.43 (0.29, 0.63)	<0.001
HMAR					
Hospital workers	n = 349	n = 381	n = 730		
	3.4 (1.8–5.9)	0.5 (0.06–1.9)	1.9 (1.1–3.2)	0.15 (0.02, 0.67)[b]	0.004
Other community members	n = 392	n = 866	n = 1,261		
	15.8 (12.4–19.8)	7.2 (5.5–9.1)	9.8 (8.3–11.6)	0.41 (0.28, 0.61)	<0.001
Amoy Gardens residents (Block E)	n = 27	n = 51	n = 78		
	37.0 (19.4–57.6)	17.7 (8.4–30.9)	24.4 (15.4–35.4)	0.36 (0.11, 1.19)	0.058
Amoy Gardens residents (non-Block E)	n = 59	n = 196	n = 255		
	22.0 (12.3–34.7)	7.7 (4.4–12.3)	11.0 (7.4–15.5)	0.29 (0.12, 0.71)	0.002
All households of all IP	n = 827	n = 1,494	n = 2,324		
	11.7 (9.6–14.1)	5.9 (4.8–7.2)	8.0 (6.9–9.1)	0.47 (0.34, 0.64)	<0.001

[a]The reference group is before March 25.
[b]Exact 95% CI.
[c]Fisher exact test p value.

factor (p = 0.88). All of these univariately significant variables except age were significant in the multivariate stepwise logistic regression (Table 5).

Factors Associated with Household Member Attack Rates

As with the household attack rate, type of index patient (OR = 5.48–16.99, Table 1), whether the individual family member had visited the index patient in the hospital (OR= 2.65), longer duration of index patient's home stay (OR = 1.72 and 3.18), and index patient's date of fever onset (later versus earlier onset date, OR = 0.48) were univariately significant factors distinguishing between the case group and the control group. Moreover, the risk for SARS transmission was greatly increased when both the individual household member and the index patient were not wearing a mask during the hospital visit, (OR = 4.16, Table 1). In the univariate analyses, variables associated with close contacts with the index patient, such as the following: whether the was the main caregiver of the index patient (OR = 2.47), whether the participant shared a room or a bed with the index patient (OR 1.66 and 3.74), frequency of dining together with the index patient (OR 1.90 and 3.82, respectively, for those having dined 5–10 times and >10 times during the period between onset of fever of index patient and his or her hospital admission) and frequency of being coughed on by the index patient within one m (OR = 1.81 and 2.47, respectively, for responses of occasionally and frequently), were also significantly associated with household member attack rates.

In the multivariate analyses, the type of index patient (hospital workers, other community workers, and the like) was associated with household member attack rates, and the directions were the same as in the univariate analyses (Table 6). Moreover, individual household members who had visited the index patient when neither the index patient nor the visitor had worn a mask were more likely to have contracted SARS, when compared to those who had not visited the index patient (OR = 3.12, Table 6). Those household members who had had occasional or frequent close contacts of <1 m with the index patient were more likely than other household members to be included in the case group (OR = 2.14 and 2.30, Table 6). The household members were also less likely to have the index patient's onset of fever occurring on or after March 25 as compared to the control group (OR= 0.51).

Discussion

Of approximately 72% of SARS cases in Hong Kong (as of May 16, 2003) that were covered by this investigation, approximately 15% of all index patient's households and 8% of all members of these households had contracted SARS. These figures include those of the Amoy Gardens residents. It is believed that the Block E transmissions had primarily resulted from environmental contamination

Table 4. Univariate analysis of associations between risk factors and Household Attack Rates

Risk factor	Any probable secondary case within the household (%)		Odds ratio (95% CI)	Chi-square p value[a]
	Yes	No		
Sex of index person (IP)				
Male (n = 400)	16.5	83.5	1.00	0.215
Female (n = 481)	13.5	86.5	0.79 (0.55 to 1.15)	
Age of IP (y)[a]				
≤30 (n = 283)	7.4	92.6	1.00	<0.001
31–40 (n = 197)	11.2	88.8	1.57 (0.84 to 2.93)	
41–50 (n = 165)	19.4	80.6	3.00 (1.67 to 5.41)	
51–60 (n = 76)	23.7	76.3	3.87 (1.94 to 7.73)	
≥61 (n = 138)	23.2	76.8	3.77 (2.08 to 6.83)	
Type of IP				
Hospital workers (n = 267)	3.7	96.3	1.00	<0.001
Amoy Gardens bock E residents (n = 36)	38.9	61.1	16.35 (6.51 to 41.08)	
Amoy Gardens other Block residents (n = 107)	19.6	80.4	6.28 (2.84 to 13.85)	
Other community members (n = 471)	18.3	81.7	5.74 (2.93 to 11.26)	
Date of IP's fever onset [b]				
Before March 25 (n = 299)	22.4	77.6	1.00	<0.001
On or after March 25 (n = 581)	11.0	89.0	0.43 (0.29 to 0.62)	
Duration IP stayed home between fever onset and hospitalization (d)[c]				
≤2 (n = 440)	9.3	90.7	1.00	<0.001
3–5 (n = 268)	15.3	84.7	1.76 (1.11 to 2.79)	
≥6 (n = 171)	28.7	71.3	3.91 (2.46 to 6.20)	
IP visited by any household member during hospitalization?				
No (n = 682)	12.6	87.4	1.00	0.001
Yes (n = 199)	22.6	77.4	2.03 (1.36 to 3.03)	
Disinfection of IP's quarters?				
Yes	15.2	84.8	1.00	0.884
No	14.7	85.3	0.96 (0.66 to 1.40)	

[a]Excluded 22 missing persons.
[b]Excluded 1 missing person.
[c]Excluded 2 missing persons.

rather than secondary infection (4,5). Excluding the Amoy Gardens cases, the attack rates were 13.9% and 8%, respectively. The SARS attack rates in the households therefore were not negligible.

The names of the probable secondary cases provided by the respondents were compared to the master list of known probable cases. A recent study, conducted by the Chinese University of Hong Kong, noted that none of the 94 asymptomatic family members of the SARS case-patients tested positive for SARS in serologic tests (unpub. data). Any underestimation due to asymptomatic transmission therefore should be minimal.

As the quarantine policy was only initiated on March 31 for the Amoy Gardens residents (12) , the median home stay was longer for earlier onset SARS cases (4 days) than the later ones (2 days). Both the household and the household member attack rates were much higher in the initial phase of the epidemic (before March 25) (10) . Moreover, between the first large-scale outbreak, which occurred approximately March 12, 2003, and March 25, 2003, relatively little was known about the disease, and hence minimal preventive measures against secondary infections were being practiced by household members (10).

Both the household and the household member attack rates of hospital healthcare workers were much lower than those of other types of households, even after controlling for other variables that were significant in the multivariate models. As compared to other households, less frequent close contacts were made in the healthcare worker households. Only 14% of the household members in the healthcare worker household had made frequent close contact (<1 m) with the index patient, as compared to 25% in the other groups ($p < 0.01$). Similarly, the percentages of dining together for >10 times during the reference period were 30.2% and 47.9%, respectively, for the healthcare worker and non-healthcare worker households ($p < 0.01$). These findings suggest that with a greater awareness and proper preventive measures, secondary attacks of SARS among household members may be greatly reduced.

Our data support the government's suggestion that environmental contamination was responsible for the large number of SARS infections in the Amoy Gardens Block E (4,5) but not in other Blocks of the Amoy Gardens. The attack rates for the Amoy Block E households were much

Table 5. Summary of stepwise multivariate logistic regression model predicting "probable secondary infection" within the household level[a]

Risk factor	Coefficient	SE	Odds ratio (95% CI)	p value
Type of Index Person (IP)				
Healthcare worker			1.00	
Amoy Gardens Block E residents	3.074	0.487	21.62 (8.33 to 56.10)	<0.001
Amoy Gardens other Block residents	1.901	0.425	6.69 (2.91 to 15.39)	<0.001
Other community member	1.705	0.354	5.50 (2.75 to 11.01)	<0.001
Date of IP's fever onset				
Before March 25			1.00	
On or after March 25	–0.696	0.235	0.50 (0.32 to 0.79)	<0.001
Duration IP stayed home between fever onset and hospitalization (d)				
≤2			1.00	
3–5	0.283	0.258	1.33 (0.80 to 2.20)	0.274
≥6	1.045	0.265	2.84 (1.69 to 4.78)	<0.001
IP visited by any household member when hospitalized?				
No			1.00	
Yes	0.483	0.242	1.62 (1.01 to 2.60)	0.046

[a]Age was not significant in the multivariable analysis.

higher than those for households of other Blocks (for later onset households, household attack rates: 36% versus 13.4%; household member attack rates: 20.8% versus 7.7%), whereas the rates of the Amoy non-Block E households were comparable to those of the "other community group" (for later onset households, household attack rates: 13.4% versus 13.1%; household member attack rates: 7.7% versus 7.2%). The observation that the median duration between the onset of symptoms in the index patient and the "first" probable secondary case of the Amoy Gardens cases were much shorter than those of the other groups also supports the environmental contamination theory that had been suggested to explain the Amoy Gardens Block E outbreak.

Our data indicate that hospital visitations to the index patient was another independent risk factor for contracting SARS, suggesting that hospital visitors may have played an important role in the SARS epidemic in Hong Kong. Among all household members who had visited an index patient in the hospital, 51 (16.5%) of 310 contracted SARS (20.3% and 8.2%, respectively, for the earlier and later onset groups). Moreover, our results demonstrated that the risk was increased when both the SARS patient and the visitor were not wearing a mask. Hence, stringent hospital

Table 6. Summary of multivariate logistic regression model predicting "probable secondary infection" of household members (N = 2,195)

Risk factor	Coefficient	SE	Odds ratio (95% CI)	p value
Type of Index Person (IP)				
Hospital care workers			1.00	
Amoy Gardens Block E residents	2.888	0.455	17.95 (7.35 to 43.83)	<0.001
Amoy Gardens other Block residents	1.661	0.419	5.26 (2.32 to 11.95)	<0.001
Other community members	1.387	0.352	4.01 (2.01 to 7.98)	<0.001
IP visited by a household member				
Not visited by any			1.00	
Both with mask	0.571	0.412	1.77 (0.79 to 3.97)	0.166
Either one with mask	0.483	0.429	1.62 (0.70 to 3.76)	0.260
Both without mask	1.139	0.326	3.12 (1.65 to 5.91)	<0.001
Frequency of close contact with IP (within 1 m)[a]				
Never			1.00	
Seldom	0.466	0.338	1.59 (0.82 to 3.09)	0.168
Occasionally	0.762	0.304	2.14 (1.18 to 3.89)	0.012
Frequently	0.834	0.288	2.30 (1.31 to 4.05)	0.004
Date of IP's fever onset				
Before March 25			1.00	
On or after March 25	–0.681	0.220	0.51 (0.33 to 0.78)	0.002
Duration IP stayed home between fever onset and hospitalization (d)				
≤2			1.00	
3–5	0.092	0.278	1.10 (0.64 to 1.89)	0.740
≥ 6	0.655	0.278	1.93 (1.12 to 3.32)	0.018

[a]Information on 13 cases and 37 controls missing.

visitation policies should be implemented and proper personal protection equipment should be required for all visitors of SARS patients.

As a longer exposure period increased the risk for secondary SARS infection among household members, clear public health messages encouraging people who develop influenza-like symptoms to seek rapid medical treatment and to use preventive measures should be disseminated. An effective surveillance system should also be able to substantially reduce the duration of home stay of the SARS patients.

The frequency of close contact is another important risk factor for household member attack rates. Together with the significant association with index patient's home stay duration, these results suggest that viral load is important in determining whether a secondary infection occurs. The results are also highly consistent with droplet theory of transmission but do not lend much support for transmission by fomites, particularly since the household attack rate was not found to be significantly associated with thorough disinfection of the living quarters.

When the data were stratified by Amoy Block E households versus other households, household disinfection was significantly associated with the household member attack rates in the former but not in the latter group (Amoy Gardens: OR = 1.11; p = 0.56, exact test; other households: OR = 0.24, p = 0.019, exact test; test for homogeneity, p = 0.013). Similar results were also obtained for the association between the household attack rate in the two groups (OR = 1.12 and 0.4, respectively, for Amoy Block E households and other households), although the association in the Amoy Block E group was not of statistical significance, possibly due to the small sample size (36 such households in total). This finding again strongly supports the claim that environmental contamination occurred in Amoy Block E households and that many of the cases were not secondary infections. Moreover, it suggests that although household disinfection was not a protective factor in the prevention of secondary infection, its role in reducing the risk for environmental infection cannot be dismissed. It is speculated that probable benefits of disinfection for protecting secondary infection might have been overridden by the effects of frequent contacts with the index patient or hospital visits.

The study has a few limitations. First, there is no way to confirm that the probable secondary infection of household members actually came from the index patient. Nosocomial infections, rather than secondary infections, may also have occurred in some of the household members during hospital visits to the index patient, but it is not possible to distinguish the two scenarios. The possibility of household members contracting the SARS virus in the community outside the home was, however, very small. Nevertheless, infection by environmental contamination has not been implicated as a large source of SARS except among Amoy Block E residents. Second, 44.6% of the time, information was provided by the household member most familiar with the household situation rather than the index patient. The households interviewed by the index patients and the households interviewed by proxy did not, however, differ in the distribution of risk factors. Moreover, most Hong Kong residents live in small apartments of <60 m^2, and many avoided going out during the SARS epidemic; the people were very sensitized to close contact to those with SARS or flu-like symptoms (10) . Hence, although the results may still be influenced by recall and reporting bias, the amount of bias should not substantially alter the findings. Third, even though recall bias may be another potential problem, almost all of the interviews were made within 3 weeks after the index patient's onset of fever; given the extremely unusual nature of SARS, respondents should have been able to reliably recall the requested information. Fourth, the study was not able to cover all SARS patients in Hong Kong, but after incorrect or unavailable contact numbers were eliminated, 78.3% of all SARS patients had been covered by this study, and the refusal rate was moderate (10.5%). Finally, the case definition of SARS was nonspecific. Data on laboratory confirmation of the SARS coronavirus were not available so it was possible that some of the cases were in fact pneumonia rather than SARS. In the later phase of the epidemic, it was possible that either case-finding became more thorough or case-finding was more specific as more information became more available. Nevertheless, it is logical to argue that the secondary attack rate declined in the later phase as the awareness was greatly heightened. It is emphasized that the figures reported in this study are probable, rather than actual attack rates.

The study, being a large-scale study investigating SARS transmission in the community setting, allows us to have a better understanding of the infectivity, modes of transmission, and prevention of SARS in a community setting. It also gives insight into the prevention of secondary SARS infection within the household.

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Lack of SARS Transmission among Healthcare Workers, United States

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Healthcare workers accounted for a large proportion of persons with severe acute respiratory syndrome (SARS) during the worldwide epidemic of early 2003. We conducted an investigation of healthcare workers exposed to laboratory-confirmed SARS patients in the United States to evaluate infection-control practices and possible SARS-associated coronavirus (SARS-CoV) transmission. We identified 110 healthcare workers with exposure within droplet range (i.e., 3 feet) to six SARS-CoV–positive patients. Forty-five healthcare workers had exposure without any mask use, 72 had exposure without eye protection, and 40 reported direct skin-to-skin contact. Potential droplet- and aerosol-generating procedures were infrequent: 5% of healthcare workers manipulated a patient's airway, and 4% administered aerosolized medication. Despite numerous unprotected exposures, there was no serologic evidence of healthcare-related SARS-CoV transmission. Lack of transmission in the United States may be related to the relative absence of high-risk procedures or patients, factors that may place healthcare workers at higher risk for infection.

The epidemic of severe acute respiratory syndrome (SARS) quickly spread worldwide in 2003. As of July 11, 2003, a total of 29 countries had reported 8,427 probable cases to the World Health Organization (1). Much of the disease worldwide was associated with hospital-based outbreaks (2,3). Healthcare workers made up a large proportion of cases, accounting for 37%–63% of suspected SARS cases in highly affected countries (4–6). In the United States, the epidemic was limited; 74 probable and 8 laboratory-confirmed case-patients were reported, despite aggressive efforts at detection, particularly in groups at high risk. Surveillance for symptoms of SARS was recommended for all healthcare workers who were exposed to patients meeting the clinical case definition for suspected or probable SARS (7).

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Due to the importance of healthcare facilities in transmission of SARS worldwide, state and local health departments, together with the Centers for Disease Control and Prevention (CDC), conducted a review of U.S. healthcare workers exposed to patients positive for SARS-associated coronavirus (SARS-CoV). Our objectives were to characterize the types of exposures and infection-control practices that occurred in U.S. hospitals related to SARS patient care and to determine the extent of SARS-CoV transmission to U.S. healthcare workers.

Methods

This investigation focused on healthcare workers at highest risk for infection, in other words, those who had known unprotected exposure to laboratory-confirmed SARS-CoV–positive patients. An exposure was defined as any healthcare worker–patient interaction that occurred within droplet range (i.e., 3 feet). Exposures were categorized as either unprotected or protected, depending upon whether full personal protective equipment was used. Full equipment was defined as the use of all the personal protective equipment recommended for the care of SARS patients, i.e., a full-length gown, gloves, N95 or higher respirator, and eye protection with goggles or a face shield (7,8).

Healthcare workers were identified by hospital infection-control practitioners and public health officials through informal interviews with hospital staff, by review of employee records, and by self-identification. In addition to the healthcare workers at highest risk, other healthcare workers of interest were included, such as those with multiple protected exposures and any who requested inclusion because of concerns about exposure.

This investigation was conducted as part of the public health response to the SARS outbreak. Informed consent was obtained from healthcare workers before epidemiologic and clinical information and biologic specimens were collected. A standardized questionnaire was used to collect data on demographics, occupation, exposure characteristics, use of personal protective equipment, patient events to which the healthcare workers were exposed (e.g.,

coughing or vomiting), and presence during medical procedures. In addition, information was collected regarding any clinical signs or symptoms in the worker up to 10 days after exposure, including fever, cough, shortness of breath, or radiographically confirmed pneumonia. A single convalescent-phase serum sample was collected from healthcare workers at least 28 days after their last exposure to the patient. In some situations early in the outbreak, samples were collected between days 22 to 28 early in the outbreak, consistent with CDC recommendations at the time. Serum samples were tested for anti–SARS-CoV serum antibodies by enzyme-linked immunosorbent assay (ELISA) and indirect fluorescent antibody test (9).

Data were entered into Microsoft Access and statistical analysis was performed with SAS version 8.2 (SAS Institute, Cary, NC). Univariate analysis was performed by using two-sided Fisher exact or Mantel-Haenszel chi-squared test, as appropriate. A p value of <0.05 was considered significant.

Results

Eight of the nine United States healthcare facilities in which SARS-CoV–infected patients were evaluated participated in the investigation. Six of the eight SARS-CoV–positive patients visited or were hospitalized at these eight facilities. A total of 110 healthcare workers (range 4–36 healthcare workers per healthcare facility) participated in this follow-up investigation (Table 1). This total represented approximately 85% of healthcare workers who were identified as being at high risk for infection. Healthcare workers were exposed to these patients from March 15 to June 23, 2003.

The median age of healthcare workers was 41 years (range 23–61), 75% were females, and 74% were Caucasian (Table 2). The most common occupation was nursing staff (48%), and the most common work site was the medical ward (38%), followed by the emergency department (24%) (Table 2). Preexisting medical conditions in the healthcare workers were infrequent (data not shown).

Table 2. Demographic characteristics, occupation, and location of participating HCWs exposed to laboratory-confirmed SARS patients (n = 110)[a]

Characteristic	n (%)
Median age	41 (range 23–61)
Female gender	82 (75)
Caucasian	81 (74)
Nursing staff[b]	53 (48)
Technicians[c]	23 (21)
Medical staff[d]	16 (15)
Other occupation	18 (16)
Medical ward	41 (38)
Emergency department	26 (24)
Outpatient clinic	16 (15)
Intensive care unit	7 (6)
Other location	20 (18)

[a]HCWs, healthcare workers; SARS, severe acute respiratory syndrome.
[b]Nursing staff, registered nurses, licensed practicing nurses, nurses aides, patient care technician.
[c]Technicians, respiratory therapist, phlebotomist, radiology technician.
[d]Medical staff, residents, fellows, attending physician, physician assistants.

Each healthcare worker was exposed over a median of 2.0 days (range 1–14), during which a median of 3.0 interactions (range 1–50) with the SARS patient occurred. Of the 102 healthcare workers from whom complete data were available, 45 (44%) reported exposure without any type of mask; 72 (70%) had exposure without eye protection (Table 3).

Sixty-six healthcare workers (65%) reported that the patient was coughing during one or more patient-worker interactions. Of these, 40% had at least one exposure without a respirator and 52% had at least one without gown, gloves, and eye protection. Eleven (11%) reported interaction with a patient who had active diarrhea, and 1 (1%) reported exposure during patient vomiting (Table 4). Healthcare procedures with high potential to generate droplets and aerosols were infrequent: 5 healthcare workers (5%) reported manipulating an airway, (i.e., performing endotracheal intubation or suctioning), and 4 (4%) reported being present during administration of aerosolized medications (Table 4).

Three healthcare facilities instituted full infection-control precautions (i.e., full use of personal protective

Table 1. Characteristics of SARS patient healthcare in participating U.S. healthcare facilities[a]

HCF	SARS patient	Date[b]	Date full IC[c] started	Patient-days in HCF	Participating HCWs
1	A	3/15/03	3/15/03	10	36
2	B	3/2/03	Not started	15	7
3	C	3/14/03	3/16/03	8	16
4	D	3/20/03	3/20/03	8	7
5	E	4/6/03	Not started	1	4
6	E	4/10/03	Not started	1	7
7	E	4/14/03	4/14/03	7	21
8	F	5/27/03	Not started	4	12

[a]SARS, severe acute respiratory syndrome; HCF, healthcare facility; IC, infection control; HCWs, healthcare workers.
[b]Date, refers to the first date of the visit at the healthcare facility. This may be the date of admission or the date of visit to an outpatient clinic, emergency room, laboratory, or radiology suite.
[c]Full infection control consists of negative-pressure isolation, N95 or higher respirator, gown, gloves, and eye protection.

Table 3. Personal protective equipment use in HCWs reporting droplet-range exposure (within 3 feet) to a laboratory-confirmed SARS patient (n = 102)[a]

Non-use of personal protective equipment	n (%)
Without any mask	45 (44)
Without N95 or higher respirator	49 (48)
Without eye protection	72 (70)
Direct contact without gloves	40 (39)

[a]HCWs, healthcare workers; SARS, severe acute respiratory syndrome.

equipment and placement in an isolation room) on the first day the patient was seen. Healthcare workers in these facilities reported significantly fewer unprotected exposures, in comparison to facilities where full SARS precautions were not instituted on the first day (62% vs. 87%, $p < 0.05$).

To assess adherence to infection-control practices, we identified healthcare workers who had all of their exposures only after full SARS precautions were started. We identified 43 such workers, representing all of the healthcare facilities that instituted precautions. In these workers, lapses in infection control still occurred, with nearly half reporting unprotected exposures, including many with no eye protection (Table 5).

Table 4. Healthcare workers reporting exposure to a laboratory-confirmed SARS patient according to patient events, healthcare procedures, and concurrent use of personal protective equipment (n = 102)[a]

Procedure or patient event	Total HCWs	Without respirator (%)	Without gown, gloves, and eye protection (%)
Coughing	66	27 (40)	34 (52)
Diarrhea	11	4 (36)	6 (55)
Airway manipulation	5	NA	NA
Aerosolized medication	4	1 (25)	1 (25)
Resuscitation	1	NA	NA
Bronchoscopy	1	0 (0)	0 (0)

[a]SARS, severe acute respiratory syndrome; HCWs, healthcare workers; NA, not available due to incomplete reporting.

Clinical signs or symptoms developed in 17 healthcare workers (15%) after exposure to one of the laboratory-confirmed SARS patients, most commonly cough (Table 6). Convalescent-phase serum samples were available for 103 (94%) healthcare workers; none (0%) tested positive for SARS-CoV.

During the outbreak, CDC recommended furlough for any exposed healthcare worker in whom symptoms developed within 10 days of last exposure. Fifteen healthcare workers in this review (14%) were excluded from all or selected duties as a result of SARS exposure. Of these, seven reported symptoms (fever, respiratory symptoms, or radiographically confirmed pneumonia), and eight were asymptomatic. However, 10 symptomatic healthcare workers were not excluded from duty, including four nurses or nurses' aides and one physician.

Discussion

While healthcare-related outbreaks of SARS forced hospital closings and mandatory quarantines in some countries, no such events were reported in the United States. Our investigation demonstrates that although many U.S. healthcare workers had unprotected exposures, no documented transmission of SARS-CoV was found. In light of the numerous healthcare workers in our investigation with unprotected droplet-range exposures, lack of transmission in U.S. hospitals may have resulted from a relative absence of highly infectious patients or high-risk patient procedures.

The mode of transmission of SARS is unclear, but evidence suggests it may be spread by large- and medium-sized droplets spread within 3 feet (5,10). Some studies show use of any mask was associated with lower odds of infection in healthcare-related clusters (10).

Globally, outbreaks among healthcare workers have occurred after exposure to certain patients or at certain points during illness (3,10–12). For example, in Singapore, five patients were identified early in the epidemic who had infected ≥10 contacts each (11). The timing of exposure to ill patients also is critical; patients may be most infectious in the second week of illness, as some data suggest peak viral shedding occurs at day 10 (13). Additionally, descriptive data suggest that severely ill patients may spread virus more efficiently, particularly if they are coughing or vomiting (12). Although coughing was frequently reported, vomiting was infrequent. In addition, patients seen in the United States, with the exception of one patient who required intubation, were generally not very ill.

Transmission may also be event-dependent. Procedures such as intubations and medication nebulizers have been associated with healthcare-related outbreaks, even among protected healthcare workers (11,12). One such cluster occurred in Toronto, where illness consistent with suspected or probable SARS developed in nine healthcare workers who cared for a patient around the time of intubation, despite use of full personal protective equipment (12). In the United States, potential droplet- and aerosol-generating procedures were infrequent: only one patient required mechanical ventilation, and few healthcare workers reported administering aerosolized medication or performing

Table 5. Unprotected exposures in healthcare workers exposed to laboratory-confirmed SARS patients after full infection-control procedures were initiated (n = 43)[a]

Exposure type	n (%)
Any unprotected exposure	21 (49)
Without eye protection	18 (42)
Without N95 or higher respirator	6 (14)
Direct contact without gloves	6 (14)

[a]SARS, severe acute respiratory syndrome.

Table 6. Outcomes of healthcare workers who were exposed to laboratory-confirmed SARS patients, United States (n = 110)[a]

Outcome[b]	n (%)
Cough	16 (15)
Shortness of breath	3 (3)
Fever	3 (3)
Pneumonia by chest radiography	1 (1)
Hospitalized	1 (1)

[a]SARS, severe acute respiratory syndrome.
[b]Each healthcare worker may have >1 outcome.

bronchoscopy. One notable exception was a worker who performed two endotracheal intubations before SARS was diagnosed. However, despite wearing only an N95 mask and gloves, this healthcare worker did not become symptomatic or seroconvert.

Our study was subject to a number of limitations. First, enrollment of both healthcare facilities and healthcare workers was incomplete. One institution in which healthcare workers were exposed to two SARS-CoV–positive patients was not included. Active surveillance performed by state and local public health officials, as well as hospital infection-control practitioners, identified no symptomatic healthcare workers among the exposed (J. Rosenberg, pers. comm.). Also, completeness of recruiting varied between institutions, although we had a high participation rate overall of approximately 85% of healthcare workers identified as being at high risk.

As in all surveys, recall bias was a concern. However, given that no healthcare workers were SARS-CoV–positive and few had symptoms, the effect of outcome on recall was probably minimal. Additionally, questions about hand hygiene and removal of personal protective equipment were not included because of concerns of overwhelming bias inherent in recalling such practices, although these factors may have been important.

Third, although most serum samples were obtained >28 days after last exposure to the SARS patient, 19 (18%) samples were obtained during days 22 to 28. These samples were primarily collected early in the outbreak when the recommendation for convalescent-phase serum collection was set for >21 days after exposure. Evidence from other studies shows that most case-patients case will seroconvert by day 20 (13). Although this ELISA is currently used as a standard criterion and has unknown sensitivity, a similar assay has been reported to have an estimated sensitivity of approximately 93%, based on clinical case definitions for probable SARS (13).

Despite the limitations of the study, a number of insights were gained from this analysis that may help prepare public health officials and clinicians for a reappearance of SARS, should it occur, or for the emergence of another infectious disease. Rapid identification and isolation of potentially infectious persons undoubtedly will help minimize exposures. Communication between public health officials and hospital infection control staff can help with efficient implementation of such control procedures.

However, current levels of adherence to infection-control practices in the United States may not be sufficient if many high-risk patients or procedures are encountered. Unprotected exposures among healthcare workers may still occur despite implementation of facilitywide infection-control precautions. Therefore, new initiatives for infection control should include measures to improve compliance with personal protective equipment overall, in addition to specifically focusing on patients and events that have the highest risk for transmission.

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Healthcare Worker Seroconversion in SARS Outbreak

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Serum samples were obtained from healthcare workers 5 weeks after exposure to an outbreak of severe acute respiratory syndrome (SARS). A sensitive dot blot enzyme-linked immunosorbent assay, complemented by a specific neutralization test, shows that only persons in whom probable SARS was diagnosed had specific antibodies and suggests that subclinical SARS is not an important feature of the disease.

The Study

Severe acute respiratory syndrome (SARS) emerged only in late 2002, but the rapid transmission of the disease worldwide within a few months has led to serious public health concerns. The putative agent of this new disease, identified in March 2003, is a novel and more pathogenic strain of the commonly occurring coronavirus (1,2). Cases were initially defined according to syndrome features in the absence of diagnostic tests (3). Knowledge of the epidemiology of SARS remains incomplete (4).

The proportion of persons infected with SARS-associated coronavirus (SARS-CoV) whose infection remained subclinical is not known. Such information is important, not only to facilitate understanding of the virulence of the virus but, more importantly to determine whether the control measures currently employed are sufficient to halt the spread of the virus. Should asymptomatic infection occur in substantial numbers, the virus may continue to spread, despite the isolation of the clinically apparent cases; however, this would result in the more rapid development of herd immunity in the community. The aim of this study was to determine the seroprevalence of anti–SARS-CoV antibodies in a population of exposed healthcare workers who worked in wards where an outbreak occurred.

At the beginning of April 2003, an outbreak of SARS (diagnosed according to prevailing World Health Organization guidelines) occurred in the surgical wards of the Singapore General Hospital. The source was initially unknown, and all staff and patients in these wards were potentially exposed and were themselves potential sources of the SARS virus. To contain the spread, healthcare workers from these wards were either quarantined in their homes for 2 weeks or sequestered with the patients and continued to look after them, adopting full reverse-barrier practices (5).

Subsequent contact tracing pointed to an index case-patient, whose infection led to 38 cases of SARS (in healthcare workers, patients, and visitors) in these wards and to another 12 cases of SARS in the rest of the hospital campus before the outbreak was brought under control 3 weeks later. Of the 200 healthcare workers in the surgical wards quarantined or sequestered, SARS developed in 17, and milder symptoms developed in a number of others, which did not qualify for a diagnosis of SARS under prevailing WHO guidelines (3).

The study was approved by the Ethics Committee of the Singapore General Hospital. All 200 healthcare workers, comprising doctors, nurses, health attendants, and receptionists in these surgical wards who were quarantined after the initial outbreak, were invited to participate. A total of 87 people volunteered. Of these, three had a history of probable SARS but had recovered sufficiently to return to work. Another group of 12 house officers, who joined the department during the week the study started, were invited to participate as negative controls because they had no prior exposure to known SARS patients. Informed consent was obtained from those who wished to take part. Participants filled out a questionnaire about symptoms experienced during the preceding weeks and donated a sample of blood by venipuncture; the serum specimen was stored at –80°C until use. Immunoglobulin (Ig) G antibodies to SARS-CoV were detected by using a dot blot enzyme-linked immunosorbent assay (ELISA) using a culture- derived, heat-inactivated virus antigen (E-E Ooi, unpub. data) at a serum dilution of 1:100. When compared to results of an indirect immunofluorescent assay in a limited study comprising 32 case-patients with clinically diagnosed SARS and 977 control serum samples collected before the SARS outbreak, sensitivity and specificity were

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100% and 99.8%, respectively. Samples that tested positive for IgG antibodies to SARS-CoV were further assayed for neutralizing antibodies by using the 50% tissue culture infective dose ($TCID_{50}$) method, similar to that previously described (6), under biosafety level 3 conditions, in serial twofold dilution, ranging from 1:10 to 1:320. The virus isolate used in this study, SARS-CoV 2003VA2774, has been previously sequenced (7) and was isolated from a patient in whom SARS was diagnosed. All assays were carried out in duplicate, and positive serum controls, obtained from a volunteer convalescent-phase SARS patient, were included in every run.

Four samples tested strongly positive by dot blot ELISA, although only three of these were positive for neutralizing antibodies with titers of 1:60, 1:60, and 1:320. All three were volunteers in whom probable SARS was diagnosed. Nine other samples tested weakly positive by the dot blot ELISA, although these samples were all negative by neutralization test. Analysis of data provided by the questionnaire showed that of the 84 exposed persons in whom SARS did not develop, 32 had combinations of various symptoms. None of them had positive chest x-ray findings.

Table. Symptoms of healthcare workers exposed to severe acute respiratory syndrome[a]

Symptoms	No. of persons
Asymptomatic	52
Systemic[b]	28
Upper respiratory tract[c]	25
Respiratory[d]	15
Gastrointestinal tract[e]	10
Musculoskeletal[f]	15

[a]Of the 87 volunteers, 32 had symptoms that were not sufficient to qualify as having probable severe acute respiratory syndrome. None of the 32 had positive chest x-ray signs.
[b]Systemic symptoms: fever, malaise, lethargy, headache.
[c]Upper respiratory tract symptoms: runny nose, sore throat, sore mouth or gums.
[d]Respiratory symptoms: cough, breathlessness, chest pain.
[e]Gastrointestinal tract symptoms: vomiting, diarrhea, abdominal colic.
[f]Musculoskeletal symptoms: muscle ache, joint aches.

Discussion

This is the first study to examine the seroprevalence of anti–SARS-CoV antibodies in a population with a high likelihood of having been exposed to the virus. The results indicate that all samples positive for neutralizing antibodies were from persons who had symptoms indicative of SARS (Table). None of the healthcare workers studied showed serologic evidence of subclinical infection. This result strongly validates the current infection control measures to contain the spread of this virus, i.e., early identification and isolation of case-patients.

The finding of dot blot–positive, but neutralizing antibody–negative, specimens could be due to several factors. We had chosen to screen the serum specimens at a low dilution to increase their sensitivity, which would then be confirmed by the serum neutralization test. False-positive reactions to the screening test is thus expected. Furthermore, these dot blot–positive specimens could be due to cross-reaction with other coronaviruses (7). Although negative findings in a small population are difficult to generalize, our results suggest that subclinical infection is not an important feature of SARS. We are currently conducting larger population studies to further investigate this finding.

In conclusion, in a population of healthcare workers who worked in surgical wards at the time of the outbreak, only those who sought treatment for probable SARS had anti–SARS-CoV antibodies, suggesting no subclinical infection. Early identification and isolation of cases are thus effective infection control methods.

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SARS among Critical Care Nurses, Toronto

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To determine factors that predispose or protect healthcare workers from severe acute respiratory syndrome (SARS), we conducted a retrospective cohort study among 43 nurses who worked in two Toronto critical care units with SARS patients. Eight of 32 nurses who entered a SARS patient's room were infected. The probability of SARS infection was 6% per shift worked. Assisting during intubation, suctioning before intubation, and manipulating the oxygen mask were high-risk activities. Consistently wearing a mask (either surgical or particulate respirator type N95) while caring for a SARS patient was protective for the nurses, and consistent use of the N95 mask was more protective than not wearing a mask. Risk was reduced by consistent use of a surgical mask, but not significantly. Risk was lower with consistent use of a N95 mask than with consistent use of a surgical mask. We conclude that activities related to intubation increase SARS risk and use of a mask (particularly a N95 mask) is protective.

Severe acute respiratory syndrome (SARS) was first recognized in Canada in early March 2003 (1). Caused by a novel strain of coronavirus, the disease was reported in more than 8,400 people globally, with cases in Asia, Europe, and North America in 2003 (2–4). SARS is associated with substantial illness and death. The case-fatality rate has been estimated at 13% for patients <60 years and 43% for those ≥60 years (5). In Canada, disease transmission has occurred predominantly among healthcare workers within the healthcare setting (1). Preventing SARS transmission to healthcare workers is therefore an important priority (6).

Little is known about SARS risk factors for healthcare workers. Determining patient care activities that pose a high risk for infection and possible protective measures for healthcare workers may inform strategies for prevention and may elucidate SARS transmission. Recommended protective equipment for healthcare workers caring for patients with SARS includes a particulate respirator mask (N95) and a goggle or face shield, gown, and gloves (7,8). One report from Hong Kong has suggested that surgical and N95 masks are protective (9), but few data exist to support the recommendations.

SARS poses a special challenge for healthcare workers who care for the critically ill. Many SARS patients are in critical care units. In a Toronto case series, 29 (20%) of 144 SARS patients were admitted to the intensive care unit (ICU) and 20 (69%) of these 29 received mechanical ventilation (10). The close interaction of staff and patients and the nature of invasive patient care activities, such as intubation and other procedures that involve potential exposure to respiratory secretions, raise important questions about the risk for healthcare workers working in critical care units.

To determine risk factors for SARS, we conducted a retrospective cohort study among nurses who worked in two critical care units in a Toronto hospital. We hypothesized that patient care activities (e.g., intubating, suctioning of endotracheal tubes, and administering nebulizers) that increase exposure to respiratory droplets are associated with an increased risk for SARS transmission and that masks protect against infection.

Methods

Study Setting and Population

Hospital A is a 256-bed community hospital that provides medical, surgical, obstetric, and pediatric care in the Greater Toronto Area. On March 7, 2003, the 42-year-old son (patient A) of the index patient in the Toronto SARS outbreak (1) was seen in the emergency department. He was admitted to the hospital's 10-bed ICU on March 8. Patient A stayed in the ICU until March 13, the date of his death due to SARS. On March 17, a 77-year-old man (patient B) who had been exposed to patient A in the emergency room on March 7 was admitted to the ICU. He stayed there until his death due to SARS on March 21. Patient C, another emergency room contact of patient A, was admitted to the hospital's 15-bed coronary care unit

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(CCU) on March 13. On March 16, he was transferred to another hospital's ICU, where he stayed until his death from SARS on March 29. Nurses who worked one or more shifts in hospital A's ICU from March 8 to 13 and from March 17 to 21 (i.e., when a SARS patient was in the unit) were included in the cohort. Similarly, nurses who worked one or more shifts from March 14 to March 16 in hospital A's CCU were included.

Measurements

We recorded the age, sex, and medical history of the nursing staff, including history of any respiratory illness, smoking, conditions that might result in immunosuppression, and use of immunosuppressive medications. Using a standardized data collection form, trained research nurses abstracted information regarding the patient care activities administered by the critical care nurses. To link particular nurses to activities performed in SARS patients' rooms, we identified nurses' signatures on patient charts by using a master list of signatures provided by the CCUs. Data collection included type and duration of patient care activities performed. The types of personal protection equipment (goggles, face shield, surgical mask, glove, gown, N95 mask) and the duration and frequency of using the equipment when caring for SARS patients were recorded. Information from the charts was then used to interview nurses about the specific care provided during their shifts. Information provided by the nurses was corroborated whenever possible by data from the charts.

Case Definition

We used Health Canada's case definition for suspected or probable SARS cases (11). A suspected case was described as fever ($\geq$38° C), cough or breathing difficulty, and one or more of the following exposures during the 10 days before onset of symptoms: close contact with a person with suspected or probable SARS, recent travel to an area with recent local SARS transmission outside Canada, recent travel or visit to an identified setting in Canada where SARS exposure might have occurred. A probable case was defined as a suspected SARS case with radiographic evidence of infiltrates consistent with pneumonia or respiratory distress syndrome or a suspected SARS case with autopsy findings consistent with pathologic features of respiratory distress syndrome without identifiable cause. The case definitions are in accordance with the World Health Organization's clinical case definitions (12). All three source patients met the definition for probable SARS cases. For this study, we assessed outcomes for each nurse from the first exposure to a source patient until 10 days (one incubation period) after the last exposure (March 8–April 3 for nurses in ICU and March 14–26 for nurses in CCU). Nurses who met the suspected or probable case definition and the three SARS source patients (patients A, B, and C) were tested for antibodies against SARS-associated coronavirus by immunofluorescence (EUROIMMUN, Luebeck, Germany).

Statistical Analysis

Fischer's exact two-sided tests were used to assess risk factors. Exact confidence intervals (CI) were reported. A Kaplan-Meier survival curve was constructed. Data were analyzed by using EpiInfo 2000 (Centers for Disease Control and Prevention, Atlanta, GA) and SAS version 8.0 (SAS Institute Inc., Cary, NC).

Results

Forty-three nurses worked at least one shift in a critical care unit where there was a patient with SARS; 37 worked in ICU and 6 in CCU. Eight nurses were infected with SARS, four who worked only in the ICU, three who worked only in the CCU, and one ICU nurse who worked one shift in the CCU. All cohort nurses were female; the mean age was 41 years (range 27–65 years). Only two nurses had a history of respiratory illness (one asthma, one bronchitis). Illness onset for the eight nurses was March 16–21. The most common symptoms included fever (8 [100%] of 8), myalgia (7 [87.5%] of 8), cough (6 [75%] of 8) and chills (6 [75%] of 8). Five nurses (62.5%) had headaches, and four (50%) had shortness of breath. Of the eight nurses, four (probable SARS case-patients) had unilateral infiltrates on chest radiograph and four (suspected SARS case-patients) had normal chest radiographs. SARS diagnosis in these eight nurses and in the three SARS source patients was confirmed by serology.

Patient Care Activities

Relative infection risk for 23 patient care activities is shown in Table 1. None of the 11 nurses who did not enter a SARS patient's room became ill. Our analysis was thus limited to the 32 nurses who entered a SARS patient's room at least once. Three patient care activities were associated with SARS infection: intubating (relative risk [RR] 4.20, 95% CI 1.58 to 11.14, $p = 0.04$); suctioning before intubation (4.20 RR, 95% CI 1.58 to 11.14, $p = 0.04$); and manipulating an oxygen mask (9.0 RR, 95% CI 1.25 to 64.9, $p \leq 0.01$).

Personal Protective Equipment

Use of personal protective equipment and history of high-risk patient care activities among SARS-infected nurses are summarized in Table 2. Relative risk for SARS infection and use of personal protective equipment is summarized in Table 3. Three (13%) of 23 nurses who consistently wore a mask (either surgical or N95) acquired SARS compared to 5 (56%) of 9 nurses who did not consistently

Table 1. Relative risk of critical care nurses acquiring SARS by patient care activity

Patient care activity	SARS attack rate (No. cases/No. exposed or unexposed) (%)		Relative risk (95% CI)	p value
	Exposed	Unexposed		
Intubation	3/4 (75)	5/28 (18)	4.20 (1.58 to 11.14)	0.04
Suctioning before intubation	3/4 (75)	5/28 (18)	4.20 (1.58 to 11.14)	0.04
Suctioning after intubation	4/19(21)	4/13(31)	0.68 (0.21 to 2.26)	0.68
Nebulizer treatment	3/5(20)	5/27 (8)	3.24 (1.11 to 9.42)	0.09
Manipulation of oxygen mask	7/14 (50)	1/18 (6)	9.00 (1.25 to 64.89)	0.01
Manual ventilation	2/7 (29)	6/25 (24)	1.19 (0.30 to 4.65)	1.00
Mouth or dental care	5/21 (24)	3/11(27)	0.87 (0.25 to 2.99)	1.00
Insertion of a nasogastric tube	2/6 (33)	6/26 (23)	1.44 (0.38 to 5.47)	0.62
Insertion of an indwelling urinary catheter	2/2 (100)	6/30(0.20)	5.00 (2.44 to 10.23)	0.06
Insertion of a peripheral intravenous catheter	3/5 (60)	5/27 (19)	3.24 (1.11 to 9.42)	0.09
Chest tube insertion or removal	0 (0)	0 (0)		
Insertion of a central venous catheter	2/6 (33)	6/26 (23)	1.44 (0.38 to 5.47)	0.62
Bathing or patient transfer	7/26 (27)	1/6 (17)	1.62 (0.24 to 10.78)	1.00
Manipulation of BiPAP mask	3/6 (50)	5/26 (19)	2.60 (0.8 to 7.99)	0.15
Administration of medication	5/23 (22)	3/ 9 (33)	0.65 (0.20 to 2.18)	0.65
Performing an electrocardiogram	4/12 (33)	4/20 (20)	1.67 (0.51 to 5.46)	0.43
Venipuncture	6/17 (35)	2/ 15 (13)	2.65 (0.63 to 11.19)	0.23
Manipulation of commodes or bedpans	3/5 (60)	5/ 27 (19)	3.24 (1.11 to 9.42)	0.09
Feeding	2/10 (20)	6/22 (27)	0.73 (0.18 to 3.02)	1.00
Debrillation	0/2 (0)	8/ 30 (0.27)		1.00
Cardiopulmonary resuscitation	0/3 (0)	8/29 (28)		0.55
Chest physiotherapy	2/7 (29)	6/25 (0.24)	1.19 (0.30 to 4.65)	1.00
Assessment of patient	6/ 23 (26)	2/ 9 (22)	1.17 (0.29 to 4.77)	1.00
Insertion of peripheral intravenous line	1/1 (100)	7/31 (23)	4.43 (2.31 to 8.50)	0.25
Endotracheal aspirate	3/12 (25)	5/ 20 (25)	1.00 (0.29 to 3.45)	1.00
Bronchoscopy	1/2 (50)	7/ 30 (23)	2.14 (0.46 to 9.90)	0.44
Radiology procedures	4/15(26)	4/17 (24)	1.13 (0.34 to 3.76)	1.00
Dressing change	1/6 (17)	7/26 (27)	0.62 (0.09 to 4.13)	1.00
Urine specimen collected	1/2 (50)	7/30 (23)	2.14 (0.46 to 9.90)	0.44
Fecal specimen collected	0/1 (0)	8/31(26)		1.00
Rectal swab obtained	0/1 (0)	8/31 (26)		1.00
Nasopharyngeal swab obtained	0/2 (0)	8/30 (27)		1.00
Other	2/5 (40)	6/27 (22)	1.80 (0.50 to 6.50)	0.58

[a]SARS, severe acute respiratory syndrome; CI, confidence interval.

wear a mask (RR 0.23, 95% CI 0.07 to 0.78, p = 0.02). The RR for infection was 0.22 (95%CI 0.05 to 0.93, p = 0.06) when nurses who always wore an N95 mask (2 SARS-infected and 14 noninfected nurses) were compared with nurses who did not wear any mask (N95 or surgical mask) consistently (5 SARS-infected and 4 noninfected nurses). The RR for infection was 0.45 (95%CI 0.07 to 2.71, p = 0.56) when nurses who always wore a surgical mask (one SARS-infected and three noninfected nurses) were compared with nurses who did not wear any mask (N95 or surgical mask) consistently (five SARS-infected and four for non-SARS nurses). The difference for SARS infection for nurses who consistently wore N95 masks and those who consistently wore surgical masks was not significant (RR 0.5, 95% CI 0.06 to 4.23, p = 0.5).

Time to Event

A Kaplan-Meier curve of the 32 nurses in the cohort who entered a SARS patient's room is shown in Figure. The figure demonstrates onset of symptoms by number of shifts worked. It shows that if all nurses had worked eight shifts, 53% of them would become infected with SARS. The probability of SARS infection was 6% (8/143) per shift worked.

Discussion

We found that critical care nurses who assisted with suctioning before intubation and intubation of SARS patients were four times more likely to become infected than nurses who did not. Manipulation of a SARS patient's oxygen mask was also a high-risk factor. Our findings support reports that exposure to respiratory secretions or activities that generate aerosols can result in SARS transmission to healthcare workers (13).

The 11 nurses in our study who did not enter a SARS patient's room did not become infected. This finding, along with the finding that respiratory care activities pose high risk, implicates either droplet or limited aerosol generation as a means of transmission to healthcare workers. The finding is compatible with the relative high risk (6%

Table 2. Summary of exposure, personal protective equipment, and participation in high-risk activities of the nurses in whom SARS developed[a]

Nurse	No. of shifts	Location of shift	Total duration of exposure to index patient[b] (min)	Personal protection used when inside SARS patient's room	Participation in high risk activities[c]
1	3	ICU	60	Gown Gloves Surgical mask	
2	3	ICU	385	Gown Gloves N95 Goggles[d]	Intubation, suctioning before intubation
3	3	ICU[e]	190	Gown[d] Gloves[d] N95[d]	Suctioning before intubation
4	5	ICU	935	Gloves Gown[d] Goggles[d] N95[d]	Intubation, suctioning before intubation
5	3	ICU	555	Gloves Gown N95 Goggles[d]	Intubation
6	2	CCU	510	None	
7	2	CCU	40	None	
8	2	CCU	510	Gloves[d]	

[a]SARS, severe acute respiratory syndrome; ICU, intensive care unit; CCU, coronary care unit.
[b]Duration of exposure is defined as time spent in a SARS patient's room.
[c]Intubation, suctioning before intubation.
[d]Indicates that use of this precaution was inconsistent (was not used on one or more occasions).
[e]Nurse 3 worked one shift in coronary care unit.

per shift worked) of critical care nurses. Our results did not implicate environmental transmission (i.e., contact through gowns) as a major risk factor. These data are in keeping with the report by Scales and colleagues, in which activities associated with droplet or limited aerosol spread were implicated as important sources of transmission (14).

We found a near 80% reduction in risk for infection for nurses who consistently wore masks (either surgical or N95). This finding is similar to that of Seto and colleagues, who found that both surgical masks and N95 masks were protective against SARS among healthcare workers in Hong Kong hospitals (9). When we compared use of N95 to use of surgical masks, the relative SARS risk associated with the N95 mask was half that for the surgical mask; however, because of the small sample size, the result was not statistically significant. Our data suggest that the N95 mask offers more protection than a surgical mask.

This study focused on critical care nurses working at the first SARS hospital outbreak in Toronto. Since use of personal protective equipment was not standardized during the study period, it was possible to assess the effect of personal protective equipment. The use of personal protective equipment was highly variable because the nurses were often unaware that their patients had SARS. Our results highlight the importance of using personal protective equipment when caring for SARS patients. We estimate that if the entire cohort had used masks consistently, SARS risk would have been reduced from 6% to 1.4% per shift.

A limitation of this study is that it is retrospective. Recall bias on the part of the critical care nurses is a possibility. We believe that by verifying the information provided (e.g., patient care activities) using medical records, and using the medical records to cue the interviewed nurses, we minimized recall bias. Any prospective evaluation (e.g., using an observer in ICU) after the initial outbreak

Table 3. Nurses' risk of acquiring SARS based on use of personal protective equipment[a]

Type of personal protective equipment	Attack rate (%) according to personal protective equipment used		Relative risk (95% CI)	2-Tailed Fisher exact p value
	Consistent	Inconsistent		
Gown	3/20 (15)	5/12 (42)	0.36 (0.10 to 1.24)	0.12
Gloves	4/22 (18)	4/10 (40)	0.45 (0.14 to 1.46)	0.22
N95 or surgical mask	3/23 (13)	5/9 (56)	0.23 (0.07 to 0.78)	0.02
N95[a]	2/16 (13)	5/9 (56)	0.22 (0.05 to 0.93)	0.06
Surgical mask[b]	1/4 (25)	5/9 (56)	0.45 (0.07 to 2.71)	0.56
N95 versus surgical mask[c]	2/16 (13)	1/4 (25)	0.50 (0.06 to 4.23)	0.51

[a]SARS, severe acute respiratory syndrome; CI, confidence interval.
[b]The comparator is use of no mask. The denominator n (total=32) changes for these comparisons as the nurses who consistently used the indicated personal protective equipment were compared to nurses who wore no masks.
[c]Consistent use of the N95 mask versus consistent use of a surgical mask. The denominator n (total=32) changes for these comparisons as the nurses who consistently used the indicated personal protective equipment were compared to the indicated unique group, rather than to the rest of the nurses.

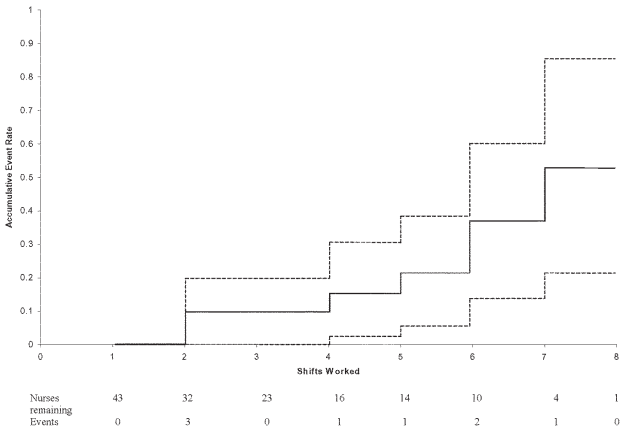

Figure. Onset of symptoms for severe acute respiratory syndrome by number of shifts worked (dashed lines represent 95% confidence limits).

would have been limited by uniformity in use of personal protective equipment (i.e., use of N95 masks, gowns, gloves, goggles). We acknowledge that the study cohort was small, and this limits inferences that can be made. Nevertheless, these data support current recommendations for use of N95 masks and for special precautions when performing intubations on SARS patients.

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Superspreading SARS Events, Beijing, 2003

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Superspreading events were pivotal in the global spread of severe acute respiratory syndrome (SARS). We investigated superspreading in one transmission chain early in Beijing's epidemic. Superspreading was defined as transmission of SARS to at least eight contacts. An index patient with onset of SARS 2 months after hospital admission was the source of four generations of transmission to 76 case-patients, including 12 healthcare workers and several hospital visitors. Four (5%) case circumstances met the superspreading definition. Superspreading appeared to be associated with older age (mean 56 vs. 44 years), case fatality (75% vs. 16%, p = 0.02, Fisher exact test), number of close contacts (36 vs. 0.37) and attack rate among close contacts (43% vs. 18.5%, p < 0.025). Delayed recognition of SARS in a hospitalized patient permitted transmission to patients, visitors, and healthcare workers. Older age and number of contacts merit investigation in future studies of superspreading.

One of the most intriguing aspects of coronavirus-associated severe acute respiratory syndrome (SARS) has been the circumstances under which virus is transmitted to large numbers of persons. One so-called superspreading event occurred in a Hong Kong hotel, when transmission from an ill traveler from Guangdong led to export of the virus to several other countries (1). Another highly effective episode of viral transmission occurred onboard China Air's flight 112 from Hong Kong to Beijing on March 15, 2003 (2). Superspreading also played major roles in transmission of SARS within Singapore (3) and Toronto (4). The potential to transmit SARS-associated coronavirus (SARS-CoV) to large numbers of contacts is likely influenced by factors associated with the host, agent, and environment. To develop hypotheses for future international evaluation of this issue, reviewing the circumstances of transmission associated with individual superspreading events may be useful.

Beijing experienced the largest outbreak of SARS, with >2,500 cases reported between March and June 2003 (2). Several instances of superspreading were recognized during the Beijing epidemic, including two associated with imported cases, from Guangdong and Hong Kong, that each proved critical to the rapid increase in cases (2). Epidemiologic investigation of another chain of transmission that occurred early in Beijing's outbreak permitted identification of several persons who spread SARS-CoV to many others. We describe this chain of transmission and the characteristics of superspreading detected in the course of its investigation.

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Methods

Reporting

Potential cases of infectious atypical pneumonia, later called SARS, were reported by hospitals to the Beijing Center for Disease Control, which initiated epidemiologic investigations. Data sources included case report forms, epidemiologic investigation forms, and other investigation records at Beijing's Center for Disease Control.

Definitions

Cases were defined, in accordance with the "National Case Definition of Infectious Atypical Pneumonia (SARS) in China, 2003," which was updated by the China Ministry of Health on April 23, 2003. Criteria for probable and suspected SARS included travel to a SARS-epidemic area in the 2 weeks before onset of symptoms or close contact with a probable SARS patient; fever of ≥38°C; chest x-ray abnormalities; normal or decreased leukocyte count; and no response to treatment with antimicrobial drugs.

Close contacts were identified according to the "Regulation of Beijing SARS close contact isolation, quarantine, service and supply." The definition involved persons who shared meals, utensils, place of residence, a hospital room, or a transportation vehicle with a known probable or suspected SARS patient or had visited a SARS patient in a period beginning14 days before the patient's onset of symptoms. Healthcare workers who examined or treated a SARS patient or any person who had potential

contact with bodily secretions were also considered close contacts. We arbitrarily defined superspreading to occur when one SARS patient was attributed as the source of SARS in ≥8 other persons.

Epidemiologic Investigation

We investigated probable and suspected cases reported from hospitals in Beijing to understand their relationship to each other, determine the incubation period between exposure and symptom onset, and describe clinical features at the time of symptom onset. We identified and followed close contacts of SARS patients to monitor their progress. We sought clinical data for patients associated with superspreading. The chi-square statistic and where appropriate, Fisher exact test, were used to compare proportions.

Results

Initial Infection and Transmission

A 62-year-old woman (patient A) was admitted to a specialty hospital in Beijing for treatment of diabetes mellitus on February 5, 2003. The hospital treated a SARS patient in late March 2003, but specific contacts between that patient and patient A have not been identified. On April 5, 2003, fever and headache developed in patient A. Her leukocyte count was 6.4 x10^9/L, and chest x-ray showed bilateral infiltrates with pleural effusion. She was treated for possible tuberculosis. Her clinical condition deteriorated, and she died April 12. On the same day, fever and chest x-ray abnormalities developed in eight of her relatives, including her husband, sons, daughters, and son-in-law, and they were diagnosed as having probable SARS (Figure 1).

Patient A had 74 close contacts, including 25 healthcare workers, 11 relatives, 36 patients who were hospitalized in the same ward, and 2 persons who were accompanying other patients on the same ward. Among the close contacts, SARS developed in 33 of 74, for a secondary infection rate of 45% (Figure 2).

Infection and Transmission among Second-Generation Patients

The 33 second-generation patients had 98 close contacts; SARS developed in 31 (32%). Nine (27%) of the 33 second-generation patients transmitted SARS to one or more contact.

Patients B and C were in the same ward as patient A and were discharged from the hospital after patient A was diagnosed with SARS. Each of them transmitted SARS to two relatives after discharge. The secondary infection rate among their contacts was 50% (4/8).

Patients D, E, F, G, and H were also hospitalized in the same ward as patient A, for the treatment of other diseases. They remained in the hospital after patient A was diagnosed with SARS. They later caused infection among visitors and some persons who accompanied them during their hospital stay. This hospital had not implemented isolation and quarantine procedures for SARS during this period.

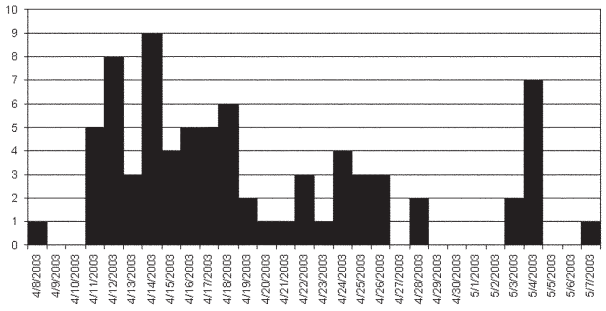

Figure 1. Epidemic curve of probable cases of severe acute respiratory syndrome, by date of onset of illness in one chain of transmission, Beijing 2003.

Patient D (associated with superspreading) is a 70-year-old woman whose symptoms developed on April 13. She had five close contacts among her relatives; SARS did not occur in any of them. On April 12, patient L was admitted to the hospital for head trauma and placed in the same room as patient D. Patient L had 15 relatives who made frequent visits to the room; SARS developed in 10 of these, presumably from contact with patient D in the shared room. Among patient L's family visitors to the room, the attack rate was 66.7% (10/15). Among all the visitors to the room (for patients D and L), the attack rate was 50% (10/20).

Patient H (associated with superspreading) is a 69-year-old woman whose symptoms developed on April 11, including chest x-ray with bilateral infiltrates. SARS developed in 8 of her 11 close contacts (secondary infection rate 73%). The second-generation patients E, F, and G

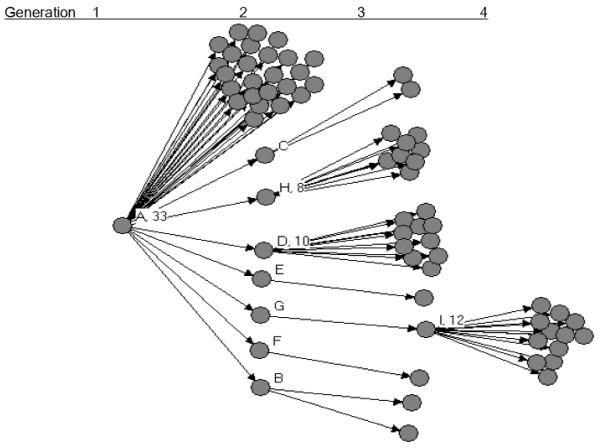

Figure 2. Probable cases of severe acute respiratory syndrome by source of transmission in chain of 77 cases in Beijing, 2003.

each had one close contact; SARS developed in all three contacts.

Three additional persons (patients J, K, and Q) had been accompanying patients on the ward; symptoms of SARS developed in these three persons in the period April 12–18. Two of these (patients J and K) transmitted SARS to three contacts each. The other 22 second-generation patients had 32 close contacts; none developed SARS.

Infection and Transmission among Third-Generation Patients

The 31 third-generation patients had 54 close contacts. Patient I was the only one who transmitted to others. Patient I, a 23-year-old man who had close contact with patient G, had onset of symptoms on April 25; unilateral abnormalities became visible on chest x-ray during the course of his illness. He had 45 close contacts with whom he either worked or lived; SARS occurred in 12 of these. The secondary attack rate among contacts of patient I was 27%.

Outcomes of Illness among Patients in Infection Chain

A total of 77 SARS patients were in this chain of transmission, including 15 who died (including index case-patient A), for a case-fatality ratio of 20%. Case fatality was similar between the second and third generations (7/31, or 23%, second-generation patients, vs. 6/33, or 18%, third-generation patients). All deaths occurred among persons >40 years of age. Case-patients who died averaged 63 years of age (range 41 to 82); surviving patients averaged 40 years (range 17 to 80) ($p < 0.001$).

Analysis of Epidemiology of Superspreading

Among the 77 patients, 66 did not transmit to others, and 7 transmitted to ≤3 contacts. In contrast, four persons (patients A, D, H, and I) transmitted to ≥8 others and were designated as associated with superspreading. The pattern of transmission is shown in Figure 3.

We compared the four case-patients associated with superspreading to the 73 other patients whose circumstances were associated with less frequent or no transmission. Patients linked to superspreading tended to be older than others in this transmission chain (mean 56 vs. 44.2 years) and a higher proportion were women (3/4 vs. 30/73, 41%, not significant by Fisher exact test). Three (75%) of four superspreaders died from their infection, compared with 12 (16%) of 73 others ($p = 0.02$, Fisher exact test, two tailed). Overall, healthcare workers accounted for 12 (16%) of the cases in this transmission chain, similar to the proportion of healthcare workers in the Beijing epidemic as a whole (16%) (2). None of the superspreading events involved transmission from healthcare workers.

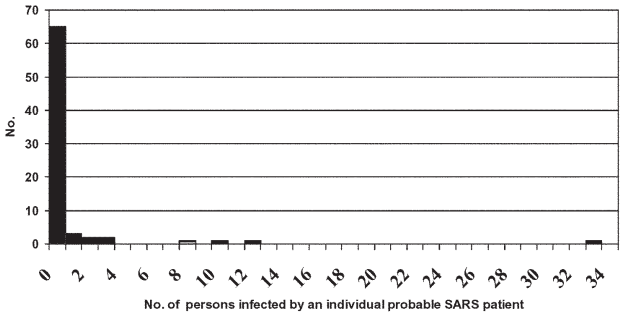

Figure 3. Number of direct secondary cases from probable cases of severe acute respiratory syndrome in one chain of transmission in Beijing, 2003.

We attempted a comparison of the number of close contacts of the index patient in superspreading events with the number of close contacts of other SARS patients; we also compared the proportion of close contacts in whom SARS developed for these two groups. Case-patients associated with superspreading averaged 36 contacts (range 11–74) while others averaged only 0.37 contacts. SARS developed in an average of 43% of close contacts of the four case-patients associated with superspreading; the syndrome developed in 18.5% of close contacts of the other patients. Thus superspreading appeared to be associated with a greater number of contacts and SARS developed in a higher proportion of those contacts ($p < 0.025$). These comparisons do not incorporate the susceptibility of contacts, but it is likely that the contacts of patient A represented a vulnerable population, since 36 (49%) of her 74 contacts were other hospitalized patients, while contacts of the later generation patients were primarily persons accompanying or visiting patients. Of note, five patients (B, C, E, F, G) who transmitted SARS to only 1–2 close contacts each had relatively few close contacts (range 1–4), which suggests limited opportunities for transmission instead of intrinsic differences in the transmissibility of their illness.

The epidemic curve for cases in this chain of transmission is shown in Figure 1. The three peaks of cases correspond to 1) second-generation patients, exposed to the index patient A (peak April 12–14), with a mean incubation period of 5.7 days; 2) third-generation patients (peak April 22–26); and 3) fourth-generation patients, peak May 4, all of whom had contact with patient I.

Cases clearly clustered in the hospital and within household members. The 77 cases involved 8 households and 1 construction site. There were 47 cases that represented secondary infection within households or workplaces, accounting for 61.3% of all patients. Seven of the eight families (77.8%) had more than two members with SARS. Sixty-two patients (81%) were either in the hospital before the onset of SARS or accompanied patients hospitalized on the same ward. Thus, even though there was transmission

within most families, the place that family members were exposed in most of these cases was the hospital. Three of four superspreading events in this transmission chain occurred within the hospital; transmission from patient I was associated with a crowded construction site.

Discussion

Our investigation highlights several features of SARS transmission observed in multiple outbreaks, including the central role of hospitals in disease transmission, the difficulty in distinguishing SARS from other clinical symptoms, and the danger associated with delayed case detection and isolation. Our investigation suggests that superspreading was related to both the environment (e.g., hospitals where large numbers of contacts occur) and host (patients who were older and had more severe illness). This transmission chain occurred relatively early in Beijing's outbreak, and hospital authorities had not yet introduced personal protective equipment or isolation of patients with respiratory conditions.

The index patient in this report had been hospitalized for 2 months before clinical symptoms of SARS began. Early detection of SARS cannot simply focus on emergency room or outpatient encounters, since nosocomial infection may be the first indication of a cluster of illness. The patient's condition was originally diagnosed as tuberculosis, another syndrome notable for potential for nosocomial transmission. Had they been implemented, appropriate respiratory precautions and patient isolation for suspected TB might have reduced hospital transmission of SARS. Improved infection-control standards for other conditions may benefit SARS control, and vice versa.

Transmission in three of the four superspreading events we describe occurred in the hospital setting. The hospital environment provided an efficient site for transmission, as was the case in other SARS outbreaks. Before administrative controls were introduced, our hospitalized patients had large numbers of contacts, including other patients, family members accompanying them during hospitalization, and other visitors. Other hospitalized patients are likely to be highly susceptible hosts because of older age and coexisting conditions. The viral load of hospitalized SARS patients is another potential factor; efficiency of SARS transmission increases in the 2nd week of illness, presumably as a function of viral load (5) or increasingly severe respiratory symptoms. The occurrence of SARS in many visitors to hospitals in Beijing and elsewhere highlights the need for administrative controls to restrict exposures to potentially infectious patients. Although not identified as factors in this transmission chain, certain aerosol-producing procedures, such as nebulizer treatments and emergency intubations, appeared to increase the risk for SARS transmission in other reports (6,7,2).

Superspreading appeared to be associated with patients who had larger numbers of close contacts as well as a higher attack rate among those contacts. These findings may be limited by bias introduced in assigning all patients hospitalized on the same ward to be contacts of the index patient. Although all case-patients were interviewed about close contacts, recall bias may have caused case-patients who were known to have transmitted to close contacts to be more thorough in identifying additional contacts. If we exclude patient A, the index patient, the average number of contacts for the three subsequent superspreading events was 24, with an attack rate among those contacts of 42%, still much higher than the corresponding numbers for other cases in this transmission chain (average 0.37 contacts and 18.5% attack rate). Although administrative controls instituted relatively late in this transmission chain reduced the number of contacts for some SARS patients, we cannot exclude the possibility that ascertainment of contacts for patients who did not transmit SARS was incomplete. In our investigation, the only example of superspreading outside the hospital setting occurred at a construction site; patient I had large numbers of contacts who worked and lived in crowded circumstances.

Superspreading was not associated with transmission from healthcare workers. Whether healthcare workers isolated themselves more promptly or had less opportunity for close contact is not known. Frequent handwashing by healthcare personnel might have contributed to lower rates of transmission. Because this outbreak occurred before personal protective equipment was routinely used, it is unlikely that use of masks or other such equipment was responsible for the low rate of transmission from healthcare workers to their contacts.

Our investigation raises hypotheses to be pursued in larger scale analysis of superspreading, such as whether demographic factors including female sex and older age are consistently associated with higher risk of transmitting to large numbers of others. Symptoms and signs evident upon illness onset should also be determined to identify clinical predictors of superspreading that might be integrated into triage protocols in the future. Additional features of the pathogen may also contribute to whether excessive transmission occurs, such as viral strain characteristics, viral load, or the presence of coinfecting organisms. Because most of the superspreaders we identified died from infection, the ability to gather additional information by retrospective interviews was limited. Future investigations will benefit from systematic and comprehensive prospective data collection from episodes of superspreading as well as comparison case circumstances.

SARS is not the only respiratory infection characterized by superspreading (8–10); other respiratory pathogens are often transmitted to large numbers of contacts.

However, the severity of illness (i.e., radiographic pneumonia) attributable to SARS may make it easier to identify transmission chains and trace back to the index case in a given community. In contrast to influenza and outbreaks of most other respiratory infections, investigation of SARS outbreaks could usually uncover an index case. The impact that superspreading played on epidemics of SARS in individual outbreaks, as well as in transporting the virus between cities, underscores the need to recognize circumstances that facilitate widespread transmission so that control measures can be targeted appropriately. Thus, while superspreading is not unique to SARS, its occurrence in outbreaks may provide a guide to establishing critical points for disease control.

The global epidemiology of SARS in 2003 was greatly influenced by the occurrence of superspreading. Although numerous countries observed imported cases of SARS, few experienced local transmission. While some of the difference between the epidemiology of SARS after importation into different countries may be the result of preparedness and prompt patient isolation, the absence of a superspreading event was likely the dominant factor influencing which countries were spared epidemic spread. Pooling of information about superspreading may help shed additional light on the special set of circumstances required to disseminate infection to large numbers of contacts.

Before better predictors of superspreading are identified, triage procedures will require aggressive infection-control management of all possible SARS patients. After prompt measures were introduced in Beijing in response to the outbreak, opportunities for superspreading were greatly reduced. Thus there may have been many other patients with host or viral characteristics conducive to superspreading later in the Beijing outbreak, but successful infection control prevented these occurrences. As this transmission chain probably represents the natural history of SARS transmission before interventions were introduced, we can use these data to estimate the probability of superspreading in a given set of patients. Four (5%) of the 77 patients characterized in this transmission chain spread to $\geq$8 others. Thus, our data suggest that in the absence of interventions, superspreading is not a common event. However, the global experience with SARS in 2003 demonstrated that a single superspreading event can initiate a cascade of events that is difficult to interrupt. Improvement of laboratory assays to recognize SARS-CoV early in the clinical course may simplify infection-control strategies for patients with suspected SARS. However at present, clinical and epidemiologic characteristics are the only factors that are initially readily available to caregivers, and these must be scrutinized carefully to assure appropriate isolation procedures.

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Atypical SARS in Geriatric Patient

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We describe an atypical presentation of severe acute respiratory syndrome (SARS) in a geriatric patient with multiple coexisting conditions. Interpretation of radiographic changes was confounded by cardiac failure, with resolution of fever causing delayed diagnosis and a cluster of cases. SARS should be considered even if a contact history is unavailable, during an ongoing outbreak.

The recent discovery of the novel severe acute respiratory syndrome–associated coronavirus (SARS-CoV) responsible for the outbreak of SARS (1–3) in China, Hong Kong, Vietnam, Singapore, Canada, and Taiwan has caused concern among the medical community because it spreads easily within the hospital environment. An unprecedented cooperative effort by the international medical research community has seen the rapid development of laboratory tests consisting of polymerase chain reaction (PCR), antibody testing, and virus isolation (4). However, before these tests were widely available, the disease was diagnosed on the basis of its clinical presentation, according to the World Health Organization (WHO) case definition (5). The presence of a fever of more than 38°C, essential and sentinel in the detection of SARS, has been described in papers from Hong Kong and Canada (1,6–8).

Nevertheless, these surveillance case definitions may not be sufficiently sensitive (9) as clinical features and epidemiologic case definitions may not coincide perfectly (10). We describe a case of SARS (with delayed diagnosis) and a consequent cluster of cases that resulted because of difficulty in establishing a positive contact history and atypical signs and symptoms.

Case Report

The patient was a 90-year-old Singaporean Chinese woman who was a resident of a nursing home. She had a past history of vascular dementia with dysphagia and behavioral abnormalities, ischemic heart disease with atrial fibrillation, and congestive cardiac failure. In addition, she also suffered from type 2 diabetes mellitus, hypertension, osteoporosis, bilateral osteoarthritis of the knees, and an old traumatic fracture of the left humeral neck. As such, she was fully dependent in her daily activities.

She was admitted to the geriatric department of Tan Tock Seng Hospital (11) on March 7, 2003, for pneumonia and urinary tract infection. These infections responded to a course of intravenous antimicrobial drugs. She also was assessed to have mild dysphagia, which required thickened fluids and blended diet without nasogastric feeding. Her chest radiograph before discharge showed persistent bilateral lower zone consolidation (Figure 1), consistent with bilateral crepitations on auscultation. However, the patient was afebrile and improved functionally to being ambulant with assistance. She was discharged to the nursing home on March 20.

Within the next two days, the patient progressively became breathless, with nausea and vomiting. There was no associated cough or diarrhea. She was eventually admitted to the medical department of Changi General Hospital, a designated non-SARS hospital, on March 25. On admission to the isolation room, she had a maximal tympanic temperature of 38.3°C, with defervescence the next day. She remained afebrile during the remainder of

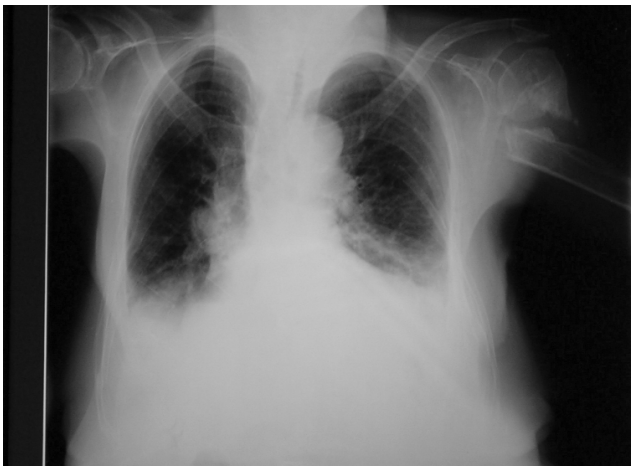

Figure 1. Chest radiograph at first admission.

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her stay. Her blood pressure was 124/84 mm Hg, pulse rate of 96 beats per minute, and respiratory rate of 32 breaths per minute. Her pulse oximetry was 100% while on 4 L per minute of intranasal oxygen. The jugular venous pressure was not elevated. Bilateral basal crepitations were heard on examination. All healthcare workers attending to the patient wore the recommended personal protective equipment, including gown, gloves, and N95 respirators, each time they entered the isolation room.

Investigations on admission showed that the patient's hemoglobin was 10.6 g/dL, leukocyte count was 7,200/mm^3 (86.3% polymorphs, 8.6% lymphocytes), and platelet count was 304,000/mm^3. The serum urea was 6.6 mmol/L; serum potassium, 5.0 mmol/L; serum sodium, 138 mmol/L; and creatinine, 79 μmol/L. The liver function tests showed a total bilirubin, 10.6 μmol/L; serum albumin, 30 g/L, serum alkaline phosphatase, 106 μ/L; serum alanine transaminase, 16 μ/L; serum aspartate transaminase, 33 μ/L. Her creatine kinase was 45 μ/L, and C-reactive protein was elevated at 147.0 mg/L. She was diagnosed to have aspiration pneumonia, and intravenous ceftriaxone and metronidazole were prescribed. Her chest radiograph showed infiltrates in the right lower zone. Her urine, sputum, and blood cultures did not yield any bacterial growth. Serologic testing for *Mycoplasma*, *Legionella*, and *Chlamydia* and nasopharyngeal aspirate for common viral antigens were not performed, as clinical suspicion was low. She was subsequently transferred to the geriatric unit. Her condition improved, and she was placed in the general ward on March 28. No protective equipment was used by staff attending her in the general ward. It was ascertained that she was previously admitted to a non-SARS ward in Tan Tock Seng Hospital.

However, on March 29, the patient became restless and more breathless. A repeat chest radiograph (Figure 2) confirmed congestive cardiac failure. Her repeat leukocyte count was 8,800/mm^3 (93.0% polymorphs, 4.5% lymphocytes), and the platelet count was 167,000/mm^3. There was mild hyponatremia (133 μmol/L) and worsening C-reactive protein levels (179.9 μg/L) but a stable creatine kinase (50 μ/L).

Intravenous diuretic therapy was instituted, but in view of her poor premorbid functional status, the patient was not intubated or moved to in an intensive care unit. She went into respiratory failure and died on March 30. Death was certified as being caused by pneumonia, with a contributing factor of ischemic heart disease. No autopsy or postmortem specimens were taken.

In the week after the patient's death, a cluster of cases of atypical pneumonia surfaced, all of which could be traced to this patient. Pneumonia developed in the patient's daughter-in-law, who had visited her in the hospital, and two grandsons living in the same household as the daughter-in-law. Another son-in-law, who met this daughter-in-law during the funeral, also contracted a respiratory illness. A healthcare worker, who was unprotected while caring for the patient, was also admitted to Changi General Hospital for severe pneumonia. He was later transferred to Tan Tock Seng Hospital where he was diagnosed with SARS. He required prolonged mechanical ventilation and eventually died of the illness. A female hospital cleaner in Changi General Hospital, who cleaned the room and tidied the patient's bed in the general ward, became symptomatic 3 days after the patient died. She was admitted to Changi General Hospital 10 days later and was transferred to Tan Tock Seng Hospital the next day. Her husband was subsequently admitted to Tan Tock Seng Hospital with SARS. All cases in the cluster had fever as a presenting complaint. On the basis of epidemiologic data (contact tracing linking her to one of the three original index cases in Singapore) (12), the index patient's cause of death was determined to be SARS (Figure 3). Serologic testing for SARS-CoV by using enzyme-linked immunosorbent assay (ELISA) techniques on various specimens during admission for febrile illness were positive at titers of 400 to 6,400 for all patients within the cluster except the patient's daughter-in-law and the healthcare worker from the nursing home.

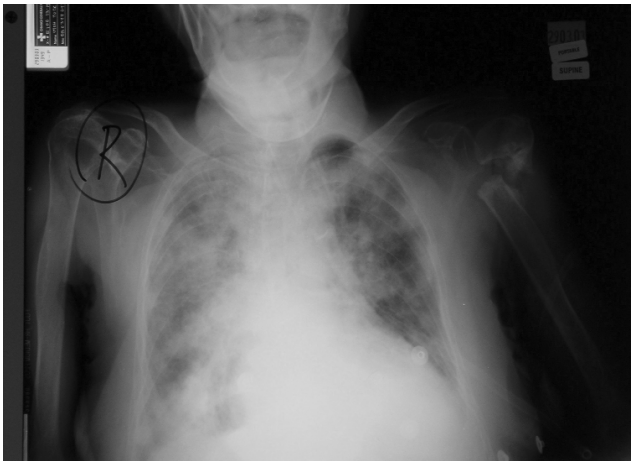

Figure 2. Repeat chest radiograph at second admission.

Conclusions

Since the issue of a global alert on atypical pneumonia by the World Health Organization on March 12, reported cases of SARS increased daily and appeared in other countries, including Canada, the United States, Europe, and Africa. The first three cases in Singapore were reported on March 13. These cases were traced to a doctor from Guangdong who infected 13 guests at a Hong Kong hotel (13). The clinical features of SARS are fairly nonspecific with a body temperature of >38°C, occurring in 100% of patients, being the most sensitive feature in all the case series published thus far, (6–8). Other symptoms

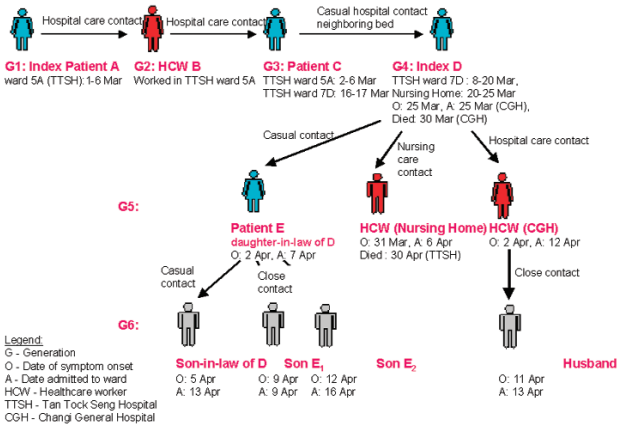

Figure 3. Cases linked to index D.

described thus far have included nonproductive cough, dyspnea, malaise, diarrhea, chest pain, headache, myalgia, and vomiting.

We describe here a fairly complicated atypical signs and symptoms of SARS in an elderly patient. The patient had a fever, which responded to a course of broad-spectrum antimicrobial drugs, thus behaving in a manner not much different from a typical community-acquired pneumonia. The absence of fever during the final course of the patient's hospitalization could have been caused by an altered immune response in the geriatric age group, with a resulting normal leukocyte count. Furthermore, prior usage of antimicrobial drugs and possible aspiration from dysphagia may further complicate detection of the disease. The suspicion of SARS in this case was thus low before eventual epidemiologic links were established retrospectively. Dyspnea is a common symptom reported previously, ranging from 60% to 80% of patients. Cough has also been noted in 80% to 100% of cases in previous studies (6,8). However the absence of cough, especially in the elderly, could be due to an underlying weak cough reflex. Vomiting, though present in our patient, was only accounted for in 10% of cases in the Canadian series (8). In a frail older person, this could also be caused by a number of circumstances.

Our patient had characteristic lymphopenia, which was seen in about 90% of reported cases. In addition, she also had mild hyponatremia and elevated C-reactive protein. However, thrombocytopenia, elevated transaminases, or raised creatine kinase levels were absent.

Serial chest radiograph progressed from a predominantly right lower lobe patchy consolidation to a radiographic picture of congestive cardiac failure. Reports from SARS cases have described mainly basal lung opacities, without any pleural effusion. An underlying poor cardiac function may masquerade the true picture of the air space disease characteristic of SARS, especially if the stress of infection decompensates left ventricular ejection fraction. This radiologic interpretation could potentially mislead clinicians and lead to more patients, family members, and healthcare workers becoming infected. In addition, a bimodal pattern of time to deterioration of clinical symptoms has been previously reported (14).

The information currently available on transmission of SARS has been attributed to respiratory droplets from close contact which has been defined by WHO to be having cared for, having lived with, or having direct contact with respiratory secretions or body fluids of a patient known to be a suspected SARS case. As the patient lived in a nursing home, the brief social contact during visits by family and friends, may prove sufficient for transmitting the virus.

Furthermore, the issue of possible coinfection and the influence of coexisting conditions have not been thoroughly investigated, which may change the clinical picture of SARS so as to conceal detection. Uncharacteristic clinical signs and symptoms, without any travel or contact history, are difficult to recognize.

Our case serves to highlight atypical signs and symptoms of SARS, especially the resolving fever, delay in establishing a positive contact history, and the nonspecific chest radiographic appearance that could be affected by concurrent coexisting conditions, such as cardiac failure. We wish to draw attention to clinicians, so that a high level of suspicion is present as the SARS-CoV is highly contagious and can cause severe disease. We observed that despite being cared for in the general ward by staff without full personal protective equipment, only one healthcare worker in Changi General Hospital was infected. This observation supports the hypothesis that the virus may not transmit effectively under certain conditions. Nevertheless, late diagnosis may lead to large clusters, as delayed isolation of suspect cases increases the risk of onward transmission in the community (15). A positive contact history may not be obvious, particularly in patients with cognitive impairment, until retrospective analysis is done. There is thus a need for continued surveillance of fever and clusters of pneumonia cases to improve the chances of early detection. Nonetheless, with the imminent availability of accurate and rapid diagnostic tests, there is hope that the diagnosis of SARS can be made with more certainty. This could be further enhanced by a revised case definition.

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Lack of SARS Transmission among Public Hospital Workers, Vietnam

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The severe acute respiratory syndrome (SARS) outbreak in Vietnam was amplified by nosocomial spread within hospital A, but no transmission was reported in hospital B, the second of two designated SARS hospitals. Our study documents lack of SARS-associated coronavirus transmission to hospital B workers, despite variable infection control measures and the use of personal protective equipment.

Vietnam was one of the first countries affected by the global severe acute respiratory syndrome (SARS) outbreak and on April 28, 2003, was the first country to be removed from the World Health Organization (WHO) list of SARS-affected countries. Sixty-one patients with laboratory-confirmed SARS were hospitalized in two hospitals, six of whom died; including the index case-patient. All case-patients were epidemiologically-linked to the index case-patient, and most outbreak amplification occurred within one hospital. We investigated whether nosocomial transmission occurred among healthcare workers in the second hospital.

The Study

The SARS outbreak in Vietnam began with the admission of a traveler from Hong Kong on February 26, 2003, to hospital A, a 56-bed, three-story, privately owned and expatriate-operated facility located in Hanoi. Within 2 weeks, extensive nosocomial transmission of SARS occurred in workers, patients, and visitors in hospital A. On March 12, hospital A was closed to new admissions except for sick hospital A workers. On that date, the 120-bed, six-story public hospital B began admitting patients with suspected and probable SARS. Hospital B treated 33 patients with laboratory-confirmed SARS between March 12 and May 2, 2003, the discharge date of the last patient (Figure). Of these, 23 were admitted directly to hospital B, and 10 were transferred from hospital A to hospital B on March 28. Many of hospital B's 33 patients were exposed to SARS as patients or visitors in hospital A.

No nosocomial SARS-associated coronavirus (SARS-CoV) transmission was reported in hospital B, and none of its 117 healthcare workers (defined as all staff working in the hospital building during the SARS outbreak) became ill with a SARS-compatible illness. This situation occurred despite obvious challenges to infection control. When hospital B began admitting patients, visitors were not tightly restricted, the main elevator was out of service, and families and workers often used the designated patient elevator. Researchers (K.C.L., H.Q.N.) and infection control advisors working daily on the hospital B wards reported variable infection control and patient isolation, particularly during the early weeks. On March 19, formal infection control training was organized and substantial technical support and supplies arrived from WHO, Médecins Sans Frontières–Belgium, and the Japan International Cooperation Agency. Systems were established to restrict visitors, and entry guards and Médecins Sans Frontières' advisors were tasked with distributing and monitoring personal protective equipment, such as N95 masks, gloves, gowns, and hand sanitizer. Two of the authors of this article (K.C.L., H.Q.N.), who worked daily on the wards observed that infection control practices improved considerably after these interventions.

To help researchers determine whether SARS-CoV transmission occurred among hospital B healthcare workers, staff were offered serologic testing from May 12 to 14

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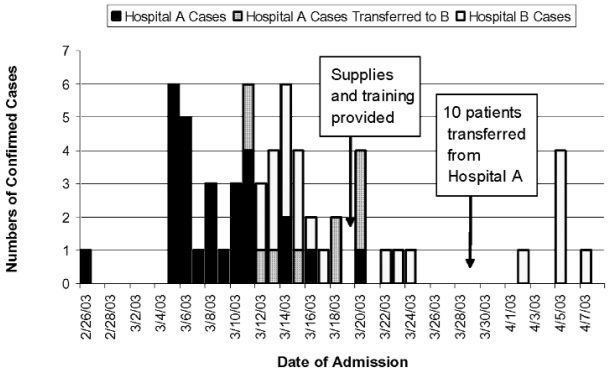

Figure. Laboratory-confirmed cases of severe acute respiratory syndrome (SARS) by date of admission, in hospital A and hospital B, Vietnam, February–April 2003. The ten case-patients who were transferred from hospital A to hospital B on March 29, 2003, are noted in gray.

and were asked to complete a short questionnaire in Vietnamese. Participants provided written consent and answered questions about demographics, level of contact with SARS case-patients, and personal protective equipment use during the busiest week of patient admissions (March 12–19) and the remaining weeks of the outbreak. Serum specimens were analyzed at the National Institute for Hygiene and Epidemiology, Hanoi, and at the Centers for Disease Control and Prevention, Atlanta, by indirect enzyme-linked immunosorbent assay (ELISA) and indirect immunofluorescence (IFA) on Vero E-6 cells infected with SARS-CoV (1). Data were double-entered into Excel and analyzed with SAS Version 8.0 (SAS, Inc., Cary, NC).

Of 117 hospital B healthcare workers, 108 participated (92.3% response rate). According to the hospital director, all 9 nonparticipants remained well, and none had a history of SARS-like illness. Among participants, 62 (57.4%) respondents worked on the SARS wards (Table). Most (85.5%) were physicians and nurses. During the first week of SARS patient care in hospital B, 39 (62.9%) of SARS ward workers reported working in SARS-patient rooms for >6 hours on their single busiest day. Of the 62 workers, 58.1% and 64.5% reported being in SARS patient rooms during medication nebulizer treatment, and 65% reported being in patient rooms during noninvasive positive pressure ventilation.

All 62 SARS ward workers reported wearing masks during the outbreak. All but one respondent wore a mask "always" or "usually" while in SARS patients' rooms. However, during the first week of SARS patient care in hospital B, 43 ward workers (69.4%) reported wearing only a cloth or surgical mask, often in combination. All 62 SARS ward workers reported using an N-95 mask after March 19, although only 56 (90.3%) reported "always" or "usually" using a mask while in SARS patients' rooms. Respondents reported using gloves 77.4% of the time before March 19 and 75.8% after March 19.

Reported symptoms and personal health behaviors of healthcare workers are also presented in the Table. One SARS ward respondent reported a fever, and less than 23% reported either a cough or sore throat. Extreme fatigue was reported by 50% of the SARS ward workers. Antibodies to SARS-CoV among our study participants were undetectable by both laboratories.

Table. Occupations, SARS exposures, symptoms, and personal protective equipment use among workers on the SARS wards, hospital B, Vietnam, May 2003[a,b]

Occupation	SARS ward respondents N (%)
Physicians	23 (37.1)
Nurses	30 (48.4)
Nonclinical staff (housekeepers, clerks, elevator operators, laboratory technicians, and guards)	9 (14.5)
Ever in room while SARS patient getting nebulized medications	36 (58.1)
Ever in room while SARS patient receiving noninvasive positive pressure ventilation	40 (64.5)
During the first week of SARS patient care (March 12–19):	
On busiest day, worked >6 hours in SARS patient's room	39 (62.9)
Wore a mask in patient's room "always" or "usually"	61 (98.4)
Wore only cloth mask, surgical mask, or both	43 (69.4)
Wore N-95 mask and other type of mask	19 (30.6)
Wore gloves in patient room "always" or "usually"	48 (77.4)
After first week of SARS patient care:	
Wore face mask in patient's room "always" or "usually"	56 (90.3)
Wore N95 mask	62 (100)
Wore gloves in patient's room "always" or "usually"	47 (75.8)
Symptoms and personal health behaviors:	
Fever	1 (1.6)
Cough	10 (16.1)
Sore throat	16 (22.6)
Extreme fatigue	31 (50)

[a]SARS, severe acute respiratory syndrome.
[b]N = 62

Conclusions

This study has several limitations. First, our survey is subject to recall and reporting bias, because not only was it difficult for respondents to recall behaviors during specific periods within the previous 2 months, but respondents may have been concerned that results could be used to evaluate their performance. Estimates of SARS exposures and the frequency of personal protective equipment use among SARS ward workers are therefore probably inflated. Second, we collected serum specimens approximately 10 to 12 days after the last SARS patients were discharged; although these patients were discharged after their 5th to 6th week of illness, the minimal chance that a patient shed virus beyond the usual 2- to 3-week period (2) would theoretically mean that a few participants may have been tested before seroconversion. A third limitation is our lack of data on hand-washing or sanitizing practices, important means of preventing respiratory virus droplet spread.

The finding of no infection with SARS-CoV among hospital B workers in the presence of 33 confirmed SARS case-patients may support the hypothesis that, in the absence of a superspreading patient or event, most SARS patients will not transmit the virus (3–6). For example, in Singapore, 81% of the first 205 reported probable case-patients had no evidence of transmission of clinically identifiable SARS to other persons (3). Over 35 healthcare workers in our study reported being exposed to a SARS patient during events that can potentially generate aerosols (i.e., nebulizer treatment or noninvasive positive pressure ventilation), yet they did not acquire SARS. Although likely many factors contributed, we demonstrated a lack of SARS transmission both before and after the provision of formal infection control training and personal protective equipment. Contrasting the hospital B situation with that of neighboring hospital A may be helpful; in hospital A, extensive transmission clusters followed admission of the index case-patient.

The 23 directly admitted hospital B patients were less severely ill than the 38 hospital A patients. In Vietnam, the best available measure of relative disease severity is the death rate and the maximal level of respiratory assistance provided. Although no hospital B patients died or received invasive mechanical ventilation; four received biphasic intermittent positive airway pressure. Seven hospital A case-patients were intubated; an additional two received biphasic intermittent positive airway pressure. Five hospital A case-patients died in Vietnam, and the index case-patient died in Hong Kong (7).

Hospital A workers did not wear masks in the earliest days after the index case-patient was admitted, although shortly after the recognition of this nosocomial cluster, enhanced infection control measures were initiated. In contrast, by the time patients were going to hospital B for evaluation, both patients and healthcare workers were wearing masks (N.T. Van, pers. comm.)

Hospital A nursing staff likely also had longer and closer contact with SARS patients. In nursing style, hospital B resembled those of other public hospitals in Vietnam, where nursing is traditionally a shared function with family members. Families of SARS patients in hospital B were observed by authors (K.C.L., N.Q.H.) to be feeding, bathing, and toileting the patients. Hospital A nurses, however, were required by hospital guidelines to assume most patient care functions traditionally shared with the patient's family (L.T. Hong, pers. comm.), thereby increasing their direct contact with SARS patients and their respiratory and other secretions. Furthermore, the more severely ill SARS patients of hospital A likely required more intensive nursing care, perhaps increasing the duration and dose of SARS-CoV exposure.

Environmental conditions at the two hospitals differed, but the impact of these differences on SARS transmission is unclear. Neither hospital had negative pressure rooms. Hospital A was a more modern facility; however, hospital B had designated SARS isolation wards and large spacious rooms with high ceilings and ceiling fans and large windows kept open for cross-ventilation. In contrast, hospital A's rooms were smaller, and individual air-conditioning units were in use early during the outbreak. In addition, hospital A had diverse patients (maternity, postoperative, pediatric, etc.) housed on the same hospital floor when the SARS outbreak began.

The findings of lack of transmission among hospital B healthcare workers raises the question of whether family caregivers or visitors might have become infected with SARS-CoV, and about the relative infectiousness of hospital B patients in general. Although overt SARS transmission to visitors occurred in hospital A, no such transmission to visitors was observed in hospital B. We lack adequate data to quantify the exposure of visitors to patients at either hospital, but the authors who were present (K.C.L., H.Q.N.) noted that after the first week, most hospital B family members tended to always wear masks and to rarely use gloves. Studies assessing the serologic status of family and community contacts of case-patients are ongoing. Although community transmission did not seem to play a major role in the Vietnam SARS outbreak, at least two episodes are known in which SARS transmission occurred outside the hospital setting. One episode involved transmission from a visitor to hospital A to five contacts. This visitor was severely ill and was later hospitalized at hospital B on day 10 after symptom onset; he is known to have transmitted infection to one contact in the 4 hours immediately before his admission. If SARS viral shedding peaks on day 10 of illness and continues for 2–3 weeks (2), we can assume that some of the hospital B patients were still

infectious during their hospitalization. Among the 23 directly admitted hospital B patients, the median days to admission was 7 (range 1–13) after illness onset.

In conclusion, we found no evidence of SARS-CoV transmission among hospital B workers, despite contact with laboratory-confirmed SARS case-patients and variable infection control practices and use of personal protective equipment. This finding may be explained by differences in infection control practices, use of personal protective equipment (including masks for patients as well as healthcare workers), nursing style, environmental features, and clinical factors such as severity of illness and the absence of a highly infectious SARS-CoV spreader. More study is needed to determine how each of these factors affects the risk of SARS transmission if we are to adequately prepare for future SARS epidemics.

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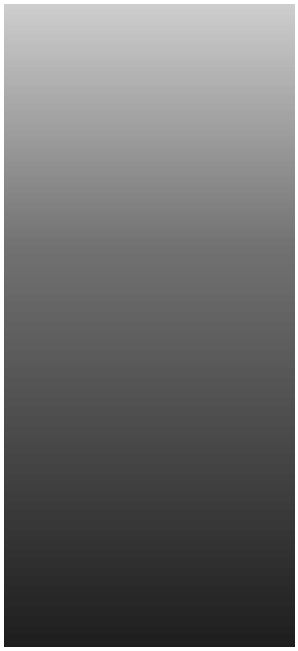

Cluster of SARS among Medical Students Exposed to Single Patient, Hong Kong

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We studied transmission patterns of severe acute respiratory syndrome (SARS) among medical students exposed exclusively to the first SARS patient in the Prince of Wales Hospital in Hong Kong, before his illness was recognized. We conducted a retrospective cohort study of 66 medical students who visited the index patient's ward, including 16 students with SARS and 50 healthy students. The risk of contracting SARS was sevenfold greater among students who definitely visited the index case's cubicle than in those who did not (10/27 [41%] versus 1/20 [5%], relative risk 7.4; 95% confidence interval 1.0 to 53.3). Illness rates increased directly with proximity of exposure to the index case. However, four of eight students who were in the same cubicle, but were not within 1 m of the index case-patient, contracted SARS. Proximity to the index case-patient was associated with transmission, which is consistent with droplet spread. Transmission through fomites or small aerosols cannot be ruled out.

Severe acute respiratory syndrome (SARS) is a newly recognized clinical entity associated with infection by a novel coronavirus (SARS-CoV) (1–4). SARS is characterized by symptoms of fever, chills, headache, and dry cough, with radiographic evidence of pneumonia in most patients. The incubation period of SARS is estimated to be a median of 4 to 6 days (range 2–10 days). SARS is contagious, and person-to-person transmission appears to occur primarily through contact or respiratory droplets (5). However, because of the efficient transmission of SARS observed in some situations (6,7), concerns remain about the spread of SARS-CoV through other means, including small aerosols or contact with contaminated environmental surfaces.

The pandemic of SARS is believed to have originated in late 2002 in Guangdong Province, China (5). A SARS patient from this region, who had onset of illness on February 15, 2003, traveled to Hong Kong and may have infected several guests at the hotel where he resided during February 21–22. One of the affected hotel guests was a resident of Hong Kong; on February 24, he exhibited an illness characterized by fever, cough, runny nose, and malaise. His symptoms worsened over the next few days, leading to his hospitalization on March 4 at the Prince of Wales Hospital, a major teaching hospital of the Chinese University of Hong Kong. The cause of this patient's illness was not recognized until March 10, when secondary cases of SARS were first reported among healthcare workers; specific infection control measures were then implemented.

Epidemiologic investigations indicate that this patient transmitted SARS to 47 healthcare workers on the ward to which he was admitted; the administration of a bronchodilator through a jet nebulizer was widely believed to have contributed to this dramatic pattern (1). SARS developed in all but one of the 16 nursing staff members on the ward and in all 6 ward physicians. The first patient with a secondary case of SARS, which presumably resulted from infection by this index patient, was not hospitalized until March 11. Therefore, the period from March 4 to 10 provided a risk window during which the factors that affected transmission of SARS among persons exposed exclusively to this index patient could be assessed.

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Although several groups of healthcare workers were exposed to SARS, some groups (e.g., ward nurses and doctors) could not provide useful information because most were affected by SARS, and other groups (e.g., staff in the accident and emergency department) could not recall all of their exposures to the index patient. However, a group of medical students who visited the ward had limited, well-defined exposures that could be accurately recalled. These included 20 third-year medical students who performed a bedside clinical assessment in the ward on the mornings of March 6 and 7, supervised by a team of assessors from the university. Each student was assigned to examine specific patients in the ward during a 40-minute interval on 1 of the 2 days. The locations (bed numbers) of the patients assigned to each student were precisely known, as well as the relative location of these patients to the index SARS case-patient. In addition to the students who appeared for the assessments, several other students (mostly fifth-year students) visited the ward for bedside teaching or clinical training March 4–10. We analyzed the epidemiologic features and patterns of transmission of SARS among these students.

Methods

Study Population

We conducted a retrospective cohort study of medical students who visited the index patient's ward from March 4 to March 10, 2003. To define the study cohort, all 474 medical students of the university who were in their clinical years (years 3–5) were contacted to inquire whether they had visited the patient's ward during this period. Because the university classes were suspended in response to the outbreak at the time this investigation was begun, the students were contacted by electronic mail.

Data Collection

Students who reported visiting the patient's ward during the period were given a detailed questionnaire that sought information about demographic characteristics, history of recent illnesses, activities in the ward (including specific exposure to the index patient), use of personal protective equipment, and history of travel March 1–10. Students who contracted SARS were interviewed in the hospital wards where they were admitted. To facilitate the recall of exposures to the index patient, a map showing the location of the index patient on the ward was distributed with the survey. Survey responses were validated by a follow-up telephone interview or electronic mail communication. Data provided by students regarding the bed numbers of patients they examined during their bedside clinical assessment were cross-checked with the university records. The medical (including nursing) records of the index patient and the students who were ill with SARS were reviewed.

Case Definition

A case of SARS was defined by the presence of fever (temperature >38°C) and evidence of pneumonia on either a radiograph or computed tomographic image of the thorax, with or without respiratory symptoms (e.g., cough and shortness of breath).

Laboratory Studies

Paired serum specimens were obtained during the acute phase and convalescent phase (day 21 from onset of fever) of illness from ill students, and single serum samples were obtained during April 26 to May 3 from students who visited the ward during March 4 to 10 but did not acquire SARS. The serum specimens were tested for anti–SARS-CoV immunoglobulin (Ig) G by indirect immunofluorescence, by using SARS-CoV–infected Vero cells fixed in acetone. A positive test was defined as either seroconversion ($\geq$4-fold rise in antibody titer in the paired serum specimens) or a convalescent-phase antibody titer of >1:40.

Ventilation Study

Information on the ward ventilation system was first obtained from the Electrical and Mechanical Services Department of the hospital. A detailed assessment of the ventilation system and airflow studies could not be performed at the time of the outbreak because of logistic constraints. Retrospective on-site inspections and measurements of the ventilation design and air distribution were carried out on July 17 and July 22. The supply and exhaust airflow rates were measured by a hood flow rate meter (APM 150) (TSI Inc., Shoreview, MN) (measurement range 24–945 L/s with an accuracy of 3%). Air velocity, air temperature, and relative humidity at all supply diffusers and exhaust grilles were measured by a portable VELOCICALC Plus air velocity meter Model 8386A (TSI Inc.). Information on the location and opening sizes of supply diffusers and exhaust grilles, as well as information on the distribution of heat sources such as lighting and the number of persons in the ward, were also collected during the site visits.

Data Analysis

Epidemiologic data were entered into a predesigned database and analyzed by using SAS Version 6.12 software (SAS Institute Inc., Cary, NC). Attack rates among persons with and without specific exposures were calculated. Dose-response relationships were also evaluated with respect to the proximity to the index patient and duration of these exposures.

Data on ventilation, temperature, relative humidity, and heat sources were analyzed by computational fluid dynamics (CFD) simulations. The industry standard CFD package, Fluent, (Fluent USA, Lebanon, NH) was used to predict (reproduce) the average airflow pattern in the ward during the outbreak, taking into consideration the effect of thermal buoyancy.

Results

Clinical Course of the Index Patient's Illness

On February 24, the index case-patient had onset of an illness characterized by fever, cough, runny nose, and malaise. His symptoms worsened over the next few days, and he sought treatment at the Accident and Emergency Department of the Prince of Wales Hospital on February 27, when he was treated as an outpatient and discharged. He visited the Accident and Emergency Department again on March 4 with the same symptoms and was admitted to a general medical ward. His fever (range 38°C–40°C) did not diminish after he received various antimicrobial drugs and persisted until March 11, when it gradually subsided. His cough was frequent, low-pitched, and unproductive, with occasional scanty, whitish sputum, and it persisted from March 4 to March 13; the cough was most severe during the first 4 days of his hospitalization, March 4–7. His chest radiograph on admission showed consolidation of the right upper lobe and patchy haziness in the right lower zone. He was weak, was given an intravenous drip, and remained bedridden during his first week of hospitalization. To relieve his respiratory symptoms, he was administered salbutamol through a jet nebulizer four times per day (at 10 a.m., 2 p.m., 6 p.m., and 10 p.m.) starting from 2 p.m. on March 6 until March 12, lasting about 30 min each time. His arterial oxygen on admission was 99%; it dropped to 95% on March 6, and gradually returned to 98% on March 12. He was identified as the index patient for the outbreak of SARS in Prince of Wales Hospital on March 12 and was transferred to an isolation room within the ward. He remained in isolation for 17 days after his symptoms subsided and was discharged on March 30. The patient was not treated with either ribavirin or steroids.

Medical Student Study

Of the 474 medical students, 334 (70.5%) responded to the survey. Of the 334 respondents, 66 (20%) reported visiting the index patient's ward during the study period. Respondents and nonrespondents did not differ in age and gender. SARS did not develop in any of the nonrespondents or in any of the respondents who did not visit the index patient's ward. A detailed survey to assess illness and exposures was completed by these 66 students, which included the group of 20 third-year medical students who performed a bedside clinical assessment, supervised by a team of assessors from the university, in the ward on March 6 and 7, and 46 other students who visited the ward for clinical training on one or more occasions from March 4 to 10. None of the 20 students who appeared for the bedside clinical assessment visited this ward after March 7 or had any contact with other SARS patients in this hospital or in the community.

Sixteen (24%) of the 66 students reported an illness that met the case definition for SARS. Their mean age was 22.3 years, and 8 (50%) were male. The mean age of the 50 other students who visited the ward but did not acquire SARS was 23.2 years, and 23 (46%) were male. The most common symptoms of illness among the patients included fever (100%), chills or rigors (94%), and headache (75%); cough and shortness of breath were reported by 38% and 33% of patients, respectively (Figure 1). All ill students were hospitalized, and one required mechanical ventilation and treatment in the intensive care unit; all recovered from the illness. The characteristics of the illness among the students were similar to those among healthcare workers presumably infected by the index patient.

Paired serum specimens were collected from 15 of the 16 students during their illnesses, and all had demonstrable IgG antibodies to SARS-CoV at a titer of >1:40 in the convalescent-phase serum. The antibody titer ranged from 1:80 to 1:1,280, with a geometric mean titer of 1:440. Antibodies to SARS-CoV were absent in the serum specimens obtained from all 50 healthy students.

The dates of onset of illness of the 16 students with SARS and the dates they visited the ward are shown in Figure 2. The student with an unusually long incubation period of 16 days visited the ward (for a 40-minute bedside clinical assessment) on March 7. On March 13, she was noted to have pneumonic changes on a chest radiograph, although she had no symptoms. She was admitted to an observation ward for suspected SARS patients (different from the index patient's ward) and was discharged on March 17 after resolution of her chest radiographic abnormalities. On March 23, fever developed, and she was

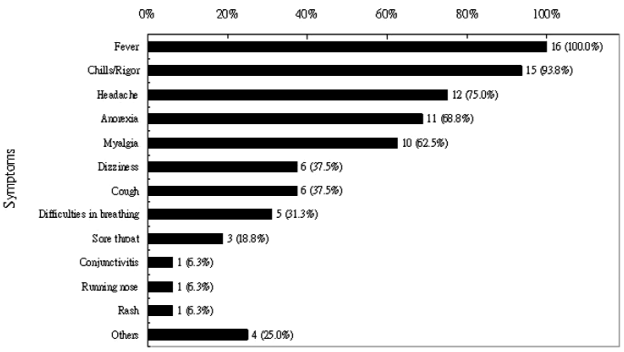

Figure 1. Distribution of initial symptoms in 16 students.

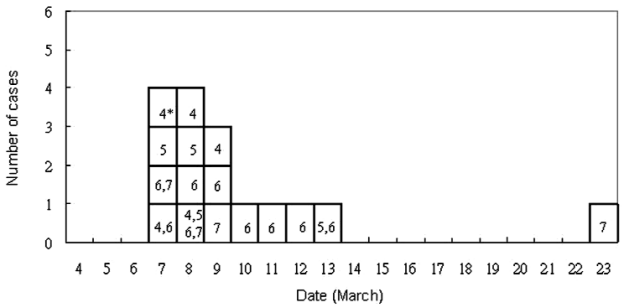

Figure 2. Dates of onset of illness of 16 students with severe acute respiratory syndrome and date of their visit to the index patient's hospital ward. An asterisk indicates the dates of the visit in March 2003.

readmitted as a potential SARS case-patient. Because we were not certain if this student had been infected during her initial exposure to the index case or during her subsequent hospitalization by exposure to another SARS patient in the observation ward, we excluded this student from the analyses of risk exposures. To obtain a precise estimate of the incubation period of SARS, we examined the onset of illness among 11 of the 16 ill students who visited the ward only on a single day, excluding the student with an incubation of 16 days. Among these 11 patients, the median incubation period was 3 days (range 2–6 days). Figure 3 shows the incubation period by onset date. Students exposed on March 6 had the widest range of incubation period (2–6 days). Too few students were exposed exclusively on other days to show any pattern.

We examined the attack rates of the illness among students based on whether they could recall entering the index patient's cubicle, a semi-enclosed section of the ward containing 10 beds (Table 1). SARS developed in 10 of the 27 students who reported entering this cubicle, compared with SARS developing in 4 of the 18 students who could not accurately recall whether they entered the patient's cubicle, and in only 1 of 20 students who reported that they never entered the cubicle (Mantel-Haenszel chi-square = 6.54; p = 0.011; Fisher exact test [2-tailed], p = 0.032). The student who did not enter the index patient's cubicle but acquired SARS was a fifth-year student (not one of the third-year students who underwent the bedside clinical assessment) who reported visiting the patient in bed no. 17x, which was located in the opposite cubicle adjacent to the corridor (Figure 4). Among those students who could recall accurately whether they entered the patient's cubicle, entering the cubicle was significantly associated with illness (10/27 versus 1/20, relative risk = 7.4, 95% confidence interval = 1.0 to 53.3, p = 0.046). The duration the students stayed in the ward was not associated with the risk for illness (mean length of stay: 67 minutes for the ill students; 80 minutes for the healthy students; p = 0.6).

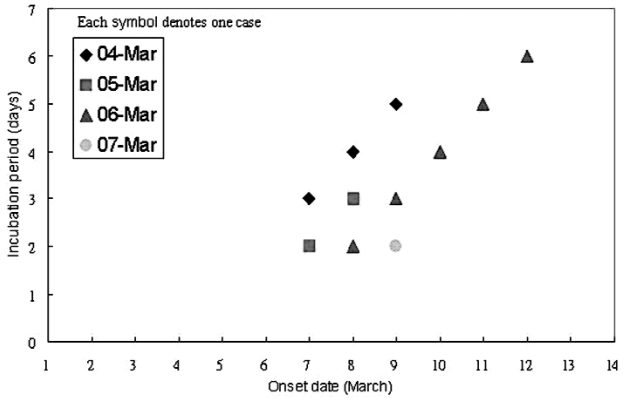

Figure 3. Incubation period by onset dates in 11 students.

Table 1. Attack rate of students by history of visit to index patient's cubicle in the ward

Entered index patient's cubicle	Ill	Not ill	Total	Attack rate (%)[a]
Yes	10	17	27	37.0
Not sure	4	14	18	22.2
No	1	19	20	5.0
Total	15	50	65	23.1

[a]Fisher exact test (2-tailed), p = 0.032; Mantel-Haenszel chi-square = 6.54; p = 0.011.

To further assess the proximity of exposure associated with illness, we analyzed data from 19 of 20 medical students (excluding the ill student who had an unusually long incubation period) who appeared for the bedside clinical assessment (lasting 40 minutes for each student) on March 6 or 7. SARS developed in 7 of these 19 students. None of the students examined the index patient. All three students who examined patients located in beds within 1 m of the index patient contracted SARS; four of eight students who examined patients located in the same cubicle but in beds >1 m from the index patient contracted SARS, but none of eight student who examined patients in other cubicles fell ill (Mantel-Haenszel chi-square = 9.86, p = 0.002; Fisher exact test [2-tailed], p = 0.0031) (Table 2; Figure 4).

As mentioned previously, the index patient was administered nebulizer therapy four times per day starting from 2 p.m. on March 6 until March 12, lasting about 30 minutes each time. Among all the students, no significant association was noted between their risk for illness and presence in the ward when the nebulizer was in use. To further study the potential role of nebulizer therapy in disease transmission, we studied the temporal patterns of illness among these 19 students who appeared for a bedside clinical assessment, excluding the student with a long incubation period (Table 3). Six out of 10 students assessed on March 6 before the nebulizer was used contracted SARS compared with 1 out of 9 students on March 7. The time of assessment of the student with SARS (on March 7) coincided with the use of the nebulizer.

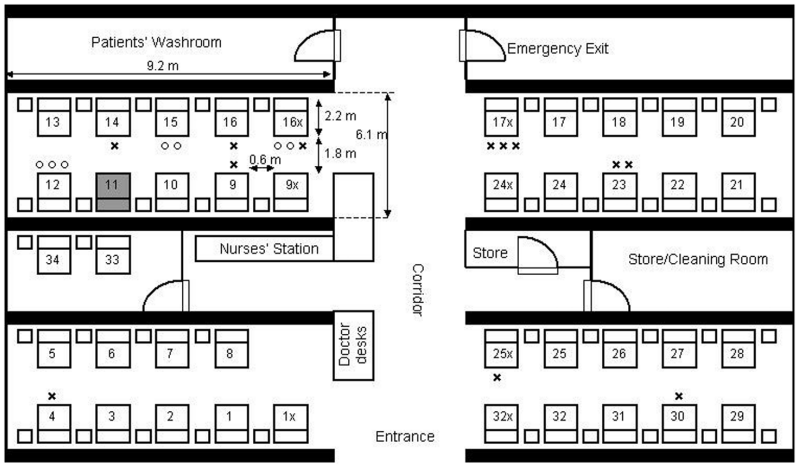

Figure 4. Floor plan of index patient's hospital ward. Numbers with and without a suffix indicate the bed numbers of patients. The bed of the index patient is shaded. 0, students assigned to examine the patient in this bed who became ill with severe acute respiratory syndrome; x, students assigned to examine the patient in this bed who remained healthy.

The medical students were assessed by a total of 11 assessors. Five assessors evaluated students on March 6 only, five on March 7 only, and one was present on both days. SARS was reported by all five assessors for March 6 only, by three of five assessors for March 7 only, and by the one assessor who was present on both days.

None of the students had traveled to mainland China, the only location with suspected community transmission of SARS during the study period. None of the ill students reported contact with another ill student or other person with SARS in the 10 days before illness onset. None wore masks or gloves while examining patients, and no notable differences in risk for disease were observed among students who reported washing their hands before and after examining patients. Apart from one hepatitis B carrier (who contracted SARS), no other students had any chronic illness. The clinical course and severity of illness in the hepatitis B carrier were similar to the experiences of other students.

Table 2. Attack rate for students attending a bedside clinical assessment in the ward in relation to their proximity to the index patient's bed[a,b]

Location of exposure	Cases/no. of students exposed
Bed nos. 10 and 12 (adjacent to index patient)	3/3
Bed nos. 9, 9x, and 13–16x (beds in the same cubicle except bed nos. 10–12)	4/8
Other beds in the ward (not in the cubicle)	0/8

[a]The index patient was not used as an assessment case.
[b]Mantel Haenszel chi-square = 9.86, p=0.002; Fisher exact test (2-tailed), p = 0.0031.

Ventilation Study

Ventilation System

The hospital is centrally air-conditioned. Fresh air is drawn from outside the hospital building into a primary air unit situated in a room adjacent to the ward, where it is cooled by chilled water and then supplied to this ward (and another ward on the opposite side of the hospital) through air ducts. The air is then distributed to five fan-coil units (one in each of the four cubicles and one at the nurses' station), where it is mixed with recirculated air, cooled by chilled water, and blown into the cubicle/nurses' station via air supply diffusers (0.6 m by 0.6 m) located at the center of the cubicle in the false ceiling and over the nurses' station. An exhaust grille, a rectangular opening 0.3 m by 0.6 m, located in the false ceiling in the corridor outside each cubicle and outside the nurses' station, recirculates 70% of the air supply back into the fan-coil unit. Excess air escapes through two extraction fans inside the toilet, two extraction fans in the store/cleaning room, and through the door of the ward to the outside.

Airflow Measurements

The air exchange was 7.79 air changes per hour for the whole ward. The supply and exhaust airflow rates are summarized in Figure 5. The total air supply was higher than the total exhaust, which meant that the ward was at a positive pressure. Our on-site measurement showed that most of the extra air supply should have exited through the ward entrance because an exhaust fan was located in both the

Table 3. Time schedule of the clinical assessment of 19 medical students[a]

Time		Ill/total
6 March 2003	10:00–10:40 a.m.	0/3
	10:40–11:20 a.m.	2/3
	11:30 a.m.–12:00 p.m.	3/3
	12:00–12:40 p.m.	1/1
7 March 2003	10:00–10:40 a.m.	1/2
	10:40–11:20 a.m.	0/3
	11:30 a.m.–12:00 p.m.	0/3
	12:00–12:40 p.m.	0/1

[a]Excluding the student-patient whose illness had a long incubation period.

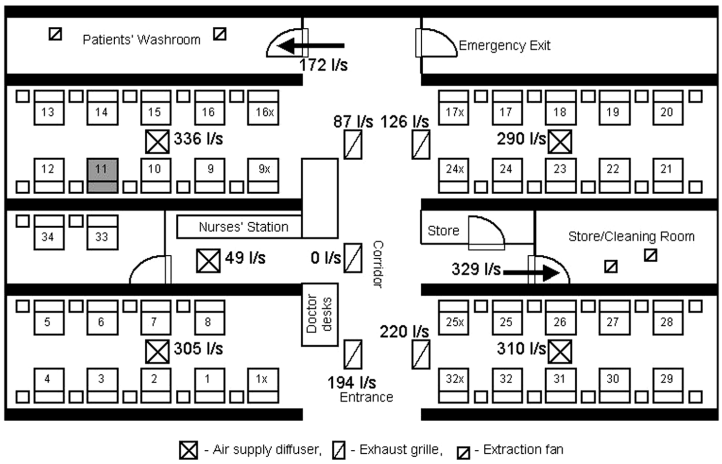

Figure 5. Airflow rates (L/s) through all air supply diffusers and exhaust grilles in the index patient's hospital ward.

primary air unit room and the kitchen, just outside the entrance to the ward; these fans would create negative pressure.

The supply and exhaust airflow rates through diffusers and exhaust grilles were found to be imbalanced. The exhaust and air supply for the nursing station did not function properly. The air supply from the diffuser in the index patient's cubicle had the highest supply flow rate (336 L/s), while the adjacent exhaust grille had the lowest exhaust flow rate (87 L/s) among all four functional exhaust grilles.

Modeling the Dispersion of Hypothetical Aerosols

At the time of the outbreak (March 4–10), the weather in Hong Kong was moderate with an ambient temperature ranging from 10.5°C to 22.3°C. The heat gains in the ward should be mainly from people, lighting, and equipment. In our computational fluid dynamics simulations to reproduce the average airflow pattern in the ward during the outbreak, we excluded the washroom and storeroom in our computational domain; and the exhaust flows through the two rooms were modeled as exhaust flows through their doorways. A free boundary condition was imposed on the ward entrance. Our computational fluid dynamics package could also consider the movement and evaporation of the aerosols. We found that aerosols would rapidly evaporate and the size of droplets would decrease rapidly after they originated from the index patient's bed. The average air speed in the room was around 0.2 m/s. The normalized concentration contours of hypothetical aerosols are shown in Figure 6. The concentrations decreased as we moved away from the index patient's bed. We also predicted a fairly high concentration profiles for beds 17x and 24x in the opposite cubicle. The concentrations in other two cubicles were almost zero.

Discussion

We utilized a unique opportunity provided by an unrecognized SARS patient who was the only known source of infection for a large cluster of secondary cases in an institutional setting to examine the transmission patterns of this novel disease. Proximity to the index case was associated with transmission, and all three students who examined the patient in bed 12 (within 1 m of the index patient) contracted SARS. As the index patient was bedridden during this period, this observation is compatible with transmission by droplets. However, that a few ill students were never within 1 m of the index patient raises the possibility of transmission by other mechanisms. Spread by contaminated fomites is a possibility, especially in light of recent data indicating that SARS-CoV survives well in the environment (8). Although none of the students reported direct contact with any of the index patient's belongings or linen, contact with other articles in the ward contaminated by the

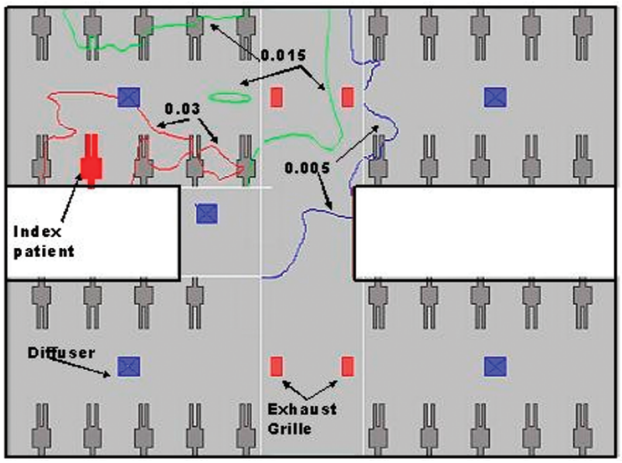

Figure 6. Dispersion of hypothetical aerosols that originated from the index patient's bed in the ward. Three levels of normalized concentrations are shown (0.03, 0.015, and 0.005) because the source strength of the virus-laden aerosols is unknown.

patient's secretions or body fluids might have occurred. Transmission by aerosols over a limited distance could also explain the observed distribution of cases and the large number of cases among healthcare workers on the ward. In our ventilation study, we found that the airflow rate was highest in the air supply diffuser in the index patient's cubicle and lowest in the corresponding exhaust grille. This imbalance and the computed concentration contours of aerosols (which match our epidemiologic data) are compatible with spread by aerosols. However, because we were not able to conduct a detailed study of ventilation patterns or conduct environmental and air sampling at the height of the outbreak due to logistic constraints, we cannot definitively assess whether either fomites or aerosols played a role in transmitting virus from the index patient.

At the time this investigation was begun, jet nebulizer therapy given to the index patient was widely believed to have facilitated transmission. However, our findings demonstrate efficient transmission even before nebulizer therapy was begun on the afternoon of March 6. First, 6 of the 10 students who attended the bedside clinical assessment on the morning of March 6 contracted SARS, compared with 1 of the 9 who attended the assessment on March 7. Second, all five of the assessors who assessed students on March 6 alone became ill, compared with three of the five assessors who were present on March 7 alone. Lastly, for the students with SARS who were present on the ward for reasons other than the bedside assessment, no association was observed between their stay in the ward at the specific periods when the nebulizer was used and the development of SARS. However, because nebulizer therapy could theoretically exacerbate symptoms of coughing in SARS patients, we recommend avoiding the use of nebulized medications and other potential aerosol-generating patient-care procedures if possible and using appropriate infection control precautions if such procedures are deemed necessary (9).

Similar large "superspreading events" of SARS associated with a single patient have been described in several countries (5,6), which contrast with the limited secondary spread seen with most SARS patients. Because many of the index patients in these clusters were infected with early cases of SARS in their respective countries, such as the index patient for this outbreak, or had subtle or atypical manifestations, the failure to recognize the disease early and institute appropriate infection control precautions might have contributed to extensive transmission. Also, some SARS patients may be intrinsically more contagious. They might excrete greater amounts of virus in their secretions or transmit virus by different routes, which may be related to specific host (e.g., altered immune status, underlying diseases), agent (e.g., coinfections with other pathogens), or environmental factors that require further study. Superspreading events have been reported in outbreaks of other diseases such as Ebola hemorrhagic fever, rubella, and β-hemolytic streptococci (10–12). While the mechanisms for these phenomena are largely unknown, possible explanations include a larger number of contacts of these superspreaders, inherent differences in the virus-host relationship, or the presence of a more virulent strain or higher levels of virus shedding (10). Similarly, hospitals have previously been documented as settings for efficient transmission of illnesses such as Lassa fever and Bolivian hemorrhagic fever (13,14).

In conclusion, this cluster demonstrates the potential for widespread nosocomial spread of SARS among a previously healthy population in the absence of specific infection control precautions. SARS is likely spread through direct contact and respiratory droplets in most instances, and others have demonstrated that specific infection control precautions to prevent transmission by these mechanisms are effective (15). However, we cannot exclude the role of contaminated fomites or small aerosols in transmitting virus in this outbreak. Whether this large cluster resulted from different mechanisms of transmission, greater viral shedding by the patient, or inadequate infection-control measures is not known, but it clearly indicates that SARS can be spread highly efficiently in some situations. A better understanding of the phenomenon of superspreading events, including clusters with apparently unique patterns (15), is key to assessing the pandemic potential of SARS and the effectiveness of control measures (16,17).

Acknowledgments

We thank all medical students, particularly the patients, for providing the data for this study.

Prof. Wong currently teaches epidemiology and public health in the Department of Community and Family Medicine, the Chinese University of Hong Kong. His research interests include viral infections (hantaviruses and SARS) and environmental health.

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Surgical Helmets and SARS Infection

James L. Derrick* and Charles D. Gomersall*

Performance testing of two brands of surgical helmets indicated that their efficiency at in vivo filtration of sub–micrometer-sized particles is inadequate for their use as respirators. These helmets are not marketed for respiratory protection and should not be used alone for protection against severe acute respiratory syndrome when performing aerosol-generating procedures.

Severe acute respiratory syndrome (SARS) is a highly contagious, potentially life-threatening condition that frequently affects healthcare workers caring for infected patients (1). Healthcare workers may need to adopt additional infection control procedures when carrying out potentially high-risk procedures such as intubation and surgery (2). These procedures can generate aerosols known to penetrate surgical masks, which may contaminate all staff in the operating room (3–5). Furthermore, other viruses such as the human papillomavirus have been shown to be present in CO_2 laser and diathermy plumes (6,7).

Surgical helmets such as the Stryker T4 (Stryker Instruments, Kalamazoo, MI) and Stackhouse FreedomAire (Stackhouse Incorporated, Palm Springs, CA) cover the entire head and use a head-mounted fan to circulate air. Unlike powered air-purifying respirators (PAPRs), which draw ambient air through a HEPA filter and blow it over the face at such a high flow rate that no unfiltered air is entrained during inspiration, surgical helmets filter air through the hood material itself. In laboratory testing, the hood material of the Stryker filters 98% of 0.1-μm particles, according to Stryker Instruments. The Stackhouse helmet has an additional filter in front of the fan, which improves the filtering capacity for 0.12-μm particles to 99.6%, according to its manufacturer.

These devices are intended to decrease contamination of the surgical wound and to protect staff from splashes of bloodborne pathogens. Although these devices are not marketed as respirators, it is natural to consider that they may be helpful in preventing respiratory transmission of SARS. The efficiency of the helmets in decreasing bacterial contamination has been tested (8); however, how well these devices protect the wearer from airborne contaminants is not known.

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Materials and Methods

We carried out a prospective, unblinded study in six healthy volunteers at the Prince of Wales Hospital in Shatin, Hong Kong. We compared the filtration capacity of the Stryker T4 and Stackhouse FreedomAire surgical helmets with an 8233 N100 filtering facepiece respirator (3M, St. Paul, MN) combined with a surgical mask and full face shield. All volunteers gave written informed consent. Approval was obtained from the Clinical Research Ethics Committee of the Chinese University of Hong Kong.

Each participant performed one test with each device. Each test measured the ability of the device to filter ambient dust particles, normally present in room air, by using a previously described standard, quantitative, fit-testing protocol (9). In brief, the testing compared particle counts inside and outside the protective device during a series of activities—normal breathing, deep breathing, turning the head from side to side, flexing and extending the head, talking loudly, and bending over followed by normal breathing.

The tube for sampling the mask particle count was connected to a test probe designed for this purpose (TSI Incorporated, St. Paul, MN), which was inserted through the fabric of the protective device. On the N100 respirator, the probe was passed through both the respirator and covering surgical mask 1 cm to the right of the valve. On the surgical helmets, the probe was placed centrally in the breathing zone 1 cm below the bottom edge of the transparent face piece. The tube for sampling the ambient particle count was fixed approximately 3 cm from the sampling probe. No participant had been previously fit tested on this brand of N100 respirator; however, all participants received instructions on donning both the respirators and the surgical helmets before use. Before each test we checked that all participants were wearing their devices correctly.

A PortaCount Plus (TSI Incorporated) connected to a computer running FitPlus for Windows software (TSI Incorporated) was used to count particles and calculate the ratio of ambient-to-device particle counts. This device counts all particles between 0.02 and 1 μm in diameter; it also calculates a fit factor, which is the average ratio of ambient-to-device particle concentrations. The equation used is

$$FitFactor = \frac{n}{\sum_{j=1}^{n} \frac{1}{ff_j}}$$

where:
n is the number of exercises performed and
ff_j is the fit factor for the individual exercise.

One modification was made to the PortaCount Plus. The reusable tubing supplied by the manufacturer was replaced with disposable polyvinyl chloride (PVC) tubing of the same internal diameter and length to minimize any risk for cross-infection. To ensure an adequate ambient particle count, the 8026 Particle Generator (TSI Incorported) was used to generate saline particles throughout the testing procedures. New hoods and masks were used for each participant. When the surgical helmet-hood combinations were being tested, the helmet and hood were put on and then a disposable surgical gown (MicroCool Specialty Gown, Kimberly-Clark, Roswell, GA) was worn over the top of the hood, in accordance with the manufacturer's instructions. Since buildup of carbon dioxide has been found to be a problem with these helmets (10), the highest fan speed was used throughout the testing. During testing of the N100 mask, the participants wore a standard three-ply surgical mask (Surgicos Johnson & Johnson, Arlington, TX) tied over the top (since the N100 mask is not licensed for use as a surgical mask) and a full face shield (Splash Shield, Woburn, MA).

The median ratios of ambient-to-device particle counts were compared by using the Mann-Whitney U test (Statview 5.0, SAS Institute, Cary, NC). A p value <0.05 was considered significant.

Results

During the tests, the median ambient concentration of 0.02 to 1 μm particles was 7,650/cm^3 (range 3,980–29,200/cm^3). Results of the filtration capacity of the three devices are shown in the Table. In all tests, the N100 mask filtered significantly more particles than either of the surgical helmet-hoods. During testing, a half-face respirator, such as the N100 mask, should reduce the particle count by a minimum of a factor of 100 (11). This minimum standard was exceeded with the N100 mask for all participants. The greatest particle count reduction achieved with a surgical helmet-hood was a factor of 4.8.

Discussion

Our data demonstrate that both surgical helmet-hoods have markedly inferior in vivo filtration performance compared to the combination of N100 mask, surgical mask, and face shield. More importantly, both surgical helmet-hoods failed in all cases to meet the National Institute for Occupational Safety and Health performance requirement for even a half-mask respirator. The requirement for a PAPR is higher. Clearly, this failure rate would be unacceptable if these devices were to be considered for use as respirators. Neither surgical helmet is approved as a respirator nor marketed as a method of protecting the user against respiratory pathogens. In fact, Stryker recommends that its helmet be used in combination with additional eye and respiratory protection in this setting (available from: URL: http://sars.medtau.org/strykerreport.doc).

Several caveats need to be applied when interpreting our data. First, we tested filtration of particles, not the coronavirus which causes SARS. In addition, it is impossible to be certain what size of particles the surgical helmet-hoods were failing to adequately filter, nor is it obvious which particle size is most important to filter, since many aerosolized particles will be larger than a naked coronavirus. It is therefore conceivable, but we believe unlikely, that the surgical helmet-hoods would efficiently filter coronavirus-containing particles. Second, we modified the PortaCount Plus by using disposable tubing rather than reusable tubing. As the disposable tubing and the

Table. Ratio of ambient-to-device concentrations of 0.02- to 1-μm–diameter particles (median [range])[a]

Exercise	Stryker T4	Stackhouse FreedomAire	3M 8233 N100 mask with surgical mask and face shield
Normal breathing	4.5 (4–5)	3 (2–4)	32,550 (1,420–60,900)
Deep breathing	4.5 (4–5)	3 (2–3)	21,550 (4,150–99,300)
Head side to side	4 (4–5)	3 (2–3)	15,675 (681–138,000)
Head up and down	4 (3–5)	3 (2–3)	19,300 (380–138,000)
Talking	4 (3–5)	3 (2–3)	1,550 (394–18,200)
Bending over	3.5 (3–4)	2 (2–3)	7,695 (1,620–31,000)
Normal breathing	4 (3–5)	2.5 (2–3)	22,100 (4,670–163,000)
Fit factor	3.8 (3.7–4.8)	2.5 (2.0–3.1)	6,392 (962–50,519)

[a]Ratios for Stryker T4 and Stackhouse FreedomAire were significantly lower in all tests compared to the combination of N100 mask, surgical mask, and face shield ($p < 0.004$).

tubing supplied by the manufacturer are both PVC, and of the same internal diameter and length, this change is unlikely to have made a difference in the results. Third, we only assessed the degree of respiratory protection provided by these devices. SARS is believed to be transmitted by contact of the virus with mucosal surfaces such as the eyes, as is the case with other respiratory viruses such as respiratory syncytial virus (12). Although both surgical helmet-hoods reduce the particle count compared to ambient counts, we believe this benefit may be counteracted by the fact that both devices direct a flow of gas into the eyes. Finally, the high particle count inside the hoods might have been due to the fan's blowing particles off the hood material, the wearer's head, or even the fan itself. In further experimentation, we found that when the surgical helmet was worn inside a PAPR system, the particle count inside the helmet was low, regardless of whether the fan was turned on or off (J. L. Derrick & C.D. Gomersall, unpub. data). It therefore seems unlikely that the particles are coming from any of these sources. Particles might also be drawn up from under the hood rather than through the hood material. In this case, the exact mechanism of entry would be irrelevant, as in both cases the indrawn air would be potentially contaminated if the patient had SARS.

Our data indicate that neither the Stryker T4 nor the Stackhouse FreedomAire helmet-hood filters enough particles of 0.02–1 μm in diameter to meet the standard for protective respirators. As the size of coronaviruses falls within this range, we recommend that neither device be used alone to protect against transmission of SARS.

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SARS Transmission among Hospital Workers in Hong Kong

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Despite infection control measures, breakthrough transmission of severe acute respiratory syndrome (SARS) occurred for many hospital workers in Hong Kong. We conducted a case-control study of 72 hospital workers with SARS and 144 matched controls. Inconsistent use of goggles, gowns, gloves, and caps was associated with a higher risk for SARS infection (unadjusted odds ratio 2.42 to 20.54, $p < 0.05$). The likelihood of SARS infection was strongly associated with the amount of personal protection equipment perceived to be inadequate, having <2 hours of infection control training, and not understanding infection control procedures. No significant differences existed between the case and control groups in the proportion of workers who performed high-risk procedures, reported minor protection equipment problems, or had social contact with SARS-infected persons. Perceived inadequacy of personal protection equipment supply, infection control training <2 hours, and inconsistent use of personal protection equipment when in contact with SARS patients were significant independent risk factors for SARS infection.

The first large-scale outbreak of severe acute respiratory syndrome (SARS) occurred on or near March 12, 2003 in the Prince of Wales Hospital in Hong Kong (1). In this worldwide epidemic, hospital workers were one of the affected groups; as of May 31, 2003, a total of 384 (22.1%) of 1,739 suspected or confirmed cases reported in Hong Kong were hospital workers (2). In the initial phase of the epidemic, hospital workers did not take special protective measures. Thus, hospital workers accounted for 43.6% (68 of 156 cases) of those admitted to the Prince of Wales Hospital from March 11 to 25, 2003 (3). By May 25, 2003, a total of 453 confirmed SARS cases had been admitted to hospitals in the New Territories East cluster of the Hospital Authority in Hong Kong, which serves 1.3 million people and to which the Prince of Wales Hospital belongs. From March 28, 2003, to May 29, 2003, a total of 77 cases of SARS infection among hospital workers had been reported by the 5 hospitals in the cluster.

A recent study concluded that the use of protective masks is an effective countermeasure against SARS (4). Nevertheless, even after these measures were implemented, there were approximately 300 more hospital workers in whom the disease developed. Limitations of that study were the small number of cases and potential confounding by the possible differences in the intensity of care given to the SARS patients between the case and control groups.

Breakthrough transmission continues despite implementing strict infection control measures. We investigated the factors associated with breakthrough transmission of the SARS virus among hospital workers infected in hospital settings.

Materials and Methods

Study Design

A 1:2 matched case-control design was used. All participants were working in wards with SARS inpatients, some of which also included non-SARS patients. The case group included all infected hospital workers in the five hospitals of the New Territories East cluster of the Hospital Authority in Hong Kong who were registered as SARS cases by the Department of Health's eSARS registry and were hospitalized during March 28 through May 25, 2003.

The SARS case definition criteria used by Hong Kong Hospital Authority is as follows: radiographic evidence of infiltrates consistent with pneumonia, and current fever >38°C or a history of such at any time in the preceding 2 days, and at least two of the following: history of chills in the past 2 days, new or increased cough or breathing difficulty, general malaise or myalgia, typical signs of consolidation, or known exposure. These criteria are equivalent with the World Health Organization's case definition for probable SARS. Suspected SARS cases are those that do not completely fulfill the above definition

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but were considered to be likely cases of SARS on the basis of clinical judgment. If no known history of exposure exists, patients are considered for exclusion if an alternative diagnosis can fully explain the clinical symptoms. Laboratory confirmation of SARS infection was also conducted by one or more of the following assays: reverse transcriptase-polymerase chain reaction (RT-PCR); culture from throat wash, urine, stool and nasal swab specimens taken at days 1, 3, and 5; or paired serologic assay from clotted blood taken at day 1 and 21.

Of 77 probable and suspected SARS cases, 72 (93.5%) participated in the study. As all staff was required to use protective masks from March 12, 2003, these hospital workers were presumed to have contracted the virus as a result of breakthrough transmission. An infection control nurse explained the purpose and logistics of the study to the study participants, obtained their verbal consent for participation, presented them with a structured questionnaire, and collected the completed questionnaire. SARS case-patients were asked to nominate as controls two colleagues who had been working in the same job position, in the same ward, and in proximity with the case-patient before he became ill. Medical and nursing staff (48 of 72 cases) self-administered the questionnaires while other staff (e.g., healthcare assistants and ward assistants) were interviewed by an infection control nurse. Out of the 72 cases, 57 nominated 114 controls who completed the questionnaire (114/144 = 79.2%); 15 cases did not nominate a control and hence 30 controls were randomly selected from the duty roster of the day before the case felt unwell, matching for job position (30/144 = 20.8%). Questionnaires were collected from 57 (79.2%) nominated controls. Nominated controls who did not return the questionnaire were replaced by controls randomly selected from the duty roster of the day before the case felt unwell, matching for job position (15/72 = 20.8%). Of the 144 controls completing the questionnaire, one was invalidated because she later became a suspected case. Controls showed neither influenzalike symptoms nor SARS-related symptoms during the study and had not been identified as a suspected SARS case as of August 15, 2003. No blood test was conducted to determine whether these persons were asymptomatic SARS cases. Another study that tested 674 healthcare workers who were working in the same hospital cluster found no asymptomatic or subclinical SARS. It can thereby be assumed that the control group had not contracted the virus (5).

Measurements

Questions were asked about the hospital worker's job position, whether the healthcare worker had been seconded from another unit, whether he/she had made physical contact with any SARS patients and if so, whether various high-risk procedures were performed to the SARS patient (including intubation, suction, cardiopulmonary resuscitation).

Personal protection equipment use (N95 mask, surgical mask, gloves, goggles, gown, and cap) was examined under three different settings: when having direct contact with SARS patients, when having contact with "patients in general" (includes both SARS and non-SARS patients), and when there was "no patient contact." Information about the frequency of using different types of personal protection equipment (never, occasionally, most of the time, or all of the time) was asked for each of these three settings. A respondent was considered to be exposed to a particular risk if he or she had "never" or "occasionally" been using personal protection equipment rather than "most or all of the time." Those who had not been in contact with any SARS patients or patients in general were considered as not having been exposed to the particular risk. Respondents were asked whether they perceived the supply of such personal protection equipment items to be adequate or not (yes/no). Questions regarding the frequency of hand washing after making contact with SARS patients, patients in general and when there was no patient contact (never, occasionally, most of the time, all of the time) were also asked. In the analysis, frequency of using personal protection equipment and frequency of hand hygiene practice were coded into 2 categories: used inconsistently (i.e., "never or occasionally used") or used consistently ("used most or all of the time").

Study participants were also asked to assess whether the masks fit them (yes/no), whether their goggles were fogged (yes/no), and the frequency of touching protective masks (never, occasionally, most of the time, or always), and whether they had any problems complying with infection control procedures (yes/no). Respondents were asked whether they had ever made social contact with others who were later found to be SARS case-patients before SARS-related symptoms manifested (yes/no/not sure), within the 14-day period before the case's onset of symptoms. The questionnaire also asked about the respondent's exposure to infection control training (length of SARS infection control training) and whether they understood the infection control measures (yes/no). A trained research assistant contacted the respondents by telephone to follow up on any incomplete or unclear answers.

Statistical Methods

Unadjusted matched odds ratios calculated from conditional logistic regression methods (6) are summarized in Tables 1 to 4. A multivariate conditional logistic regression was fitted using a forward-stepwise procedure with all variables that were marginally significant ($p < 0.10$) in the unadjusted analyses as candidates for selection. Matched odds ratios and their exact 95% confidence intervals were

derived. LogXact for Windows version 4.1 was used for all calculations (7).

Results

Background Characteristics of Respondents

The 72 SARS-infected healthcare workers worked in five hospitals (distribution: 50% Alice Ho Miu Ling Nethersole Hospital, 40.3% from Prince of Wales Hospital, 2.8% from North District Hospital, 4.2% from Shatin Hospital, and 2.8% from Taipo Hospital). The study sample was composed of nurses 59.7% (n = 43), healthcare assistants 23.6% (n = 17), medical officers 9.7% (n = 8), clerical staff (2.8%, n = 2), and workmen (4.2%, n = 3).

Use of Masks and Other Types of Protection Equipment

Almost 100% of the study respondents used either an N95 mask or surgical mask in all 3 settings (Table 1). The differences of the use of the N95 mask (most of those not

Table 1. Percentage of healthcare workers exposed to the risk of inconsistent use of different types of personal protection equipment in 3 clinical settings with SARS patients[a]

Type of personal protection equipment	Controls (n = 143)	%	Case-patients (n = 72)	%	Matched OR (exact 95% CI)	p value (exact)
N95 or Surgical mask[b]						
Direct contact with SARS patient	0	0	1	1.4	2.00 (0.05 to ∞)	0.6667
Direct contact with patients in general[c]	1	0.7	2	2.8	4.00 (0.21to 235.99)	0.5185
No patient contact[d]	3	2.2	4	5.7	2.43 (0.41 to 16.77)	0.4198
N95[b]						
Direct contact with SARS patients	6	4.2	7	9.7	2.86 (0.70 to 13.71)	0.1683
Direct contact with patients in general[e]	5	3.6	3	4.2	1.28 (0.16 to 10.47)	1.0000
No patient contact[d]	14	10.2	12	17.1	1.83 (0.72 to 4.71)	0.2315
Goggles[b]						
Direct contact with SARS patients	12	8.4	23	31.9	6.41 (2.49 to 19.49)	<0.0001
Direct contact with patients in general[e]	7	5.1	16	22.2	6.93 (2.19 to 28.85)	0.0003
No patient contact[f]	19	13.9	21	30.0	3.50 (1.42 to 9.47)	0.0046
Gown[b]						
Direct contact with SARS patients	6	4.2	15	20.8	8.85 (2.46 to 48.28)	0.0002
Direct contact with patients in general[e]	2	1.4	12	16.7	11.54 (2.56 to 106.36)	0.0002
No patient contact[f]	16	11.7	19	27.1	3.42 (1.38 to 9.30)	0.0061
Gloves[b]						
Direct contact with SARS patients	2	1.4	11	15.3	20.54 (2.96 to 887.72)	0.0002
Direct contact with patients in general[e]	5	3.6	7	9.7	3.53 (0.77 to 21.85)	0.1211
No patient contact[f]	20	14.6	19	27.1	2.42 (1.05 to 5.81)	0.0374
Cap[b]						
Direct contact with SARS patients	8	5.6	17	23.6	7.30 (2.33 to 30.21)	0.0001
Direct contact with patients in general[e]	5	3.6	15	20.8	12.81 (2.92 to 116.75)	0.0001
No patient contact"[f]	16	11.7	22	31.4	4.05 (1.68 to 10.76)	0.0009
No. of equipment inconsistently used with direct contact with SARS patients[g]						
0	129	90.2	45	62.5	1.00	
1–2	7	4.9	13	18.1	5.35 (1.79 to 18.53)	0.0015
≥3	7	4.9	14	19.4	7.84 (2.30 to 34.83)	0.0003
No. of equipment inconsistently used with direct contact with patients in general[e, g]						
0	127	92.0	52	72.2	1.00	
1–2	6	4.3	8	11.1	4.85 (1.01 to 31.86)	0.0479
≥3	5	3.6	12	16.7	10.83 (2.29 to 102.60)	0.0007
No. of equipment inconsistently used when there was no patient contact[g, h]						
0	113	82.5	46	65.7	1.00	
1–2	6	4.4	4	5.7	1.56 (0.28 to 7.97)	0.7721
≥3	18	13.1	20	28.6	3.40 (1.37 to 9.23)	0.0061

[a]SARS, severe acute respiratory syndrome; CI, confidence interval; OR, odds ratio.
[b]Those having no contact with patients were considered to be unexposed to the tabulated risk factor.
[c]Information on 4 controls missing.
[d]Information on 4 controls and 2 case-patients missing.
[e]Information on 5 controls missing.
[f]Information on 6 controls and 1 case-patients missing.
[g]Information on 6 controls and 2 case-patients missing.
[h]Including N95, goggles, gown, gloves and cap.

Table 2. Percentage with inconsistent hand hygiene[a]

Category	Controls (n = 143) n	Controls (n = 143) %	Case-patients (n = 72) n	Case-patients (n = 72) %	Matched OR (exact 95% CI)	p value (exact)
After direct contact with SARS patients	0	0	2	2.8	4.83 (0.38 to ∞)	0.2222
After direct contact with "patients in general"[b]	2	1.4	1	1.4	1.00 (0.02 to 19.21)	1.0000
When there was "no patient contact"[c]	3	2.1	10	14.3	6.38 (1.64 to 36.17)	0.0044

[a]OR, odds ratio; CI, confidence interval; SARS, severe acute respiratory syndrome.
[b]Information on 3 controls missing.
[c]Information on 1 control and 2 case-patients missing.

wearing a N95 mask were wearing a surgical mask) were not statistically significant between cases and controls in any of the three settings ($p > 0.05$, Table 1).

When hospital workers were in direct contact with SARS patients, the case group was more likely to inconsistently use goggles (odds ratio [OR] = 6.41, $p < 0.0001$), gowns (OR = 8.85, $p = 0.0002$), gloves (OR = 20.54, $p = 0.0002$), and caps (OR = 7.30, $p = 0.0001$) than the control group. When in direct contact with patients in general, cases were more likely to inconsistently use goggle (OR = 6.93, $p = 0.0003$), gowns (OR = 11.54, $p = 0.0002$), and caps (OR = 12.81, $p = 0.0001$). When there was "no patient contact," cases had more than a twofold likelihood of inconsistently using goggles ($p = 0.0046$), gowns ($p = 0.0061$), gloves ($p = 0.0374$), or cap ($p = 0.0009$), compared to their matched controls. Having three or more personal protection equipment inconsistently used (including masks) was also a significant predictor of SARS infection for hospital workers in direct contact with SARS patients (OR = 7.84, $p = 0.003$); for those with direct contact with patients in general (OR = 10.83, $p = 0.0007$); and for those with no patient contact (OR = 3.4, $p = 0.006$) (Table1).

More than 97% of both the cases and control group consistently reported to practice good hand hygiene after contacting SARS patients or "patients in general" therefore differences between the two groups were not statistically significant ($p = 0.22$, and $p = 1.00$, respectively, Table 2). There was, however, a statistically significant difference in the proportion of cases (14.3%) and controls (2.1%) of hospital workers who reported inconsistent hand hygiene when there was "no patients contact" (OR = 6.38, 95% CI = 1.64, 36.2, $p = 0.0044$).

Perceived Inadequacy of Personal Protection Equipment Supply

A much higher percentage of SARS cases compared to controls reported a perceived inadequate supply of each of the 6 types of personal protection equipment (OR = 28.0, $p < 0.0001$ for surgical masks; OR = 5.19, $p = 0.0004$ for N95 masks; OR = 8.44, $p < 0.0001$ for gowns; OR = 29.3, $p < 0.0001$ for gloves; OR = 19.8, $p < 0.0001$ for goggles; OR = 52.4, $p < 0.0001$ for cap) (Table 3). Most notably, 44.4% of the cases reported that there was an inadequate supply of at least one item of the personal protection equipment, as compared to 14.0% of the controls (OR = 6.78, $p < 0.0011$); among SARS cases, 26% reported three or more personal protection equipment items as being in inadequate supply, compared to 1.4% of the controls (OR = 52.2, $p < 0.0001$).

SARS-Related Infection Control Training

The unadjusted results indicated that 50% of SARS cases did not receive any SARS infection control training (versus 28% of the controls) (Table 4). Those who underwent ≥2 hours of training (4.2% of cases and 25.2% of controls) were far less likely to have been infected with SARS (OR = 0.03, $p < 0.0001$). Of the SARS cases, 23.9% indicated that they did not understand the infection control

Table 3. Percentages with perceived inadequacy of personal protection equipment supply and breakthrough SARS infection among hospital workers[a]

Type of personal protection equipment	Controls (n = 143) n	Controls (n = 143) %	Case-patients (n = 72) n	Case-patients (n = 72) %	Matched OR (exact 95% CI)	p value (exact)
Surgical mask	1	0.7	14	19.4	28.00 (4.26 to ∞)	<0.0001
N95 mask	13	9.1	20	27.8	5.19 (1.95 to 16.13)	0.0004
Gown	7	4.9	19	26.4	8.44 (2.77 to 34.37)	<0.0001
Gloves	2	1.4	12	16.7	29.34 (4.79 to ∞)	<0.0001
Goggles	5	3.5	22	30.6	19.81 (4.83 to 174.55)	<0.0001
Cap	4	2.8	21	29.2	52.41 (9.08 to ∞)	<0.0001
Any one of above as inadequate[b]	20	14.0	32	44.4	6.78 (2.86 to 18.51)	<0.0001
No. of items identified to be inadequate[b]						
0	123	86.0	40	55.6	1.00	
1–2	18	12.6	13	18.1	3.25 (1.17 to 9.80)	0.0209
3	2	1.4	19	26.4	52.24 (7.70 to 2280.07)	<0.0001

[a]SARS, severe acute respiratory syndrome; OR, odds ratio; CI, confidence interval.
[b]Including N95 mask, goggle, gown, gloves and cap.

measures, compared with 8.5% of the controls (OR = 3.14, p = 0.0065). Duration of SARS training (<2 hrs versus ≥2 hours) was significantly associated with reported understanding of the infection control measures (OR = 7.29, p = 0.001). There was also a marginal statistically significant difference (OR = 0.27, p = 0.057) in the proportion who reported having received updated SARS information between case-patients (88.9%) and controls (96.5%).

Patient Care and Infection Control Measures

A higher but statistically nonsignificant percentage of the control group (73.4%) reported having direct contact with SARS patients as compared to the case group (62.5%). Three (4.2%) of 72 case-patients and 7 (4.9%) of 143 controls reported that they had no direct contact with patients in general (p > 0.05). Having performed high-risk procedures on SARS patients and being seconded from another unit were not significantly associated with risk of SARS infection (Table 4).

Table 4. Percentage distributions of variables related to training, patient care, social contact and mask compliance[a]

	Controls (n = 143)		Case-patients (n = 72)			
Characteristic	n	%	N	%	Matched OR (exact 95% CI)	p value (exact)
Length of SARS infection control training						
None	40	28.0	36	50.0	1.00	
<2hrs	67	46.9	33	45.8	0.47 (0.18 to 1.14)	0.1028
≥2hrs	36	25.2	3	4.2	0.03 (0.001 to 0.20)	<0.0001
Understood infection control measures[b]						
Yes	130	91.5	54	76.1	1.00	
No	12	8.5	17	23.9	3.14 (1.35 to 7.73)	0.0065
Acquired updated information						
No	5	3.5	8	11.1	1.00	
Yes	136	96.5	64	88.9	0.27 (0.06 to 1.04)	0.0574
High risk procedures with SARS patients[c]						
No	115	86.5	60	83.3	1.00	
Yes	18	13.5	12	16.7	1.22 (0.45 to 3.14)	0.8061
Direct contact with SARS patients						
No/Not sure	38	26.6	27	37.5	1.00	
Yes	105	73.4	45	62.5	0.57 (0.28 to 1.14)	0.1197
Direct contact with patients in general						
No/Not sure	7	4.9	3	4.2	1.68	1.000
Yes	136	95.1	69	95.8	(0.07 to 117.74)	
Seconded from another unit						
No	77	53.8	46	63.9	1.00	
Yes	66	46.2	26	36.1	0.60 (0.29 to 1.21)	0.1671
Social contact with SARS patients						
No/Not sure	95	66.4	55	76.4	1.00	
Yes	48	33.6	17	23.6	0.59 (0.28 to 1.19)	0.1592
Frequency of touching the N95[d]						
Never/occasional	108	76.6	46	70.8	1.00	
Most of the time/Always	33	23.4	19	29.2	1.32 (0.63 to 2.74)	0.5205
General problems with mask[e]						
No	72	51.4	41	59.4	1.00	
Yes	68	48.6	28	49.6	0.66 (0.34 to 1.27)	0.2407
Problems with mask fit[f]						
No	73	51.0	36	52.1	1.00	
Yes	70	49.0	33	47.8	1.00 (0.51 to 1.95)	1.0000
Problems with fogging of goggles[g]						
No	67	47.2	40	60.1	1.00	
Yes	75	52.8	26	39.9	0.61 (0.31 to 1.17)	0.1520
Overall problems in general compliance[h]						
No	69	50.0	41	58.6	1.00	
Yes	69	50.0	29	41.4	0.58 (0.25 to 1.33)	0.2264

[a]OR, odds ratio; CI, confidence interval; SARS, severe acute respiratory syndrome.
[b]Information on 1 control and 1 case-patient missing.
[c]Information on 10 controls with direct contact with SARS patients missing.
[d]Excluded 2 controls and 6 case-patients who did not use N95 mask; information on 1 case-patient missing.
[e]Excluded 1 case who did not use mask; information on 3 controls and 2 case-patients missing.
[f]Excluded 1 case who did not use mask; information on 2 case-patients missing.
[g]Excluded 3 cases who did not use goggle; information on 1 control and 3 case-patients missing.
[h]Excluded 1 case who did not use any equipment; information on 5 controls and 1 case-patient missing.

There were no significant differences between the percentages of case-patients and controls who reported the following problems: general compliance problems, frequency of touching or adjusting the N95 mask, general problems with mask, problems with mask fit, and problems with fogging of goggles (Table 4).

Social Contact with SARS Cases

Approximately 23.6% of the SARS case-patients and 33.6% of the matched controls reported ever having social contact with someone who was later diagnosed with SARS before the onset of symptoms of the relevant case-patients ($p = 0.1592$) (Table 4).

Problems Encountered

Seven problems in the unadjusted analysis (Table 5) were significantly associated with risk for SARS infection. An indicator variable was constructed by counting the number of problems encountered by the study participants. Almost all (98.6%) of the case group encountered at least one problem (versus 79.9% in the control group). The risk increases greatly with the number of problems encountered (OR = 44.2 for 3 or more problems, $p < 0.0001$) (Table 5). Using a cut-off point of two or more problems to predict SARS infection gives a sensitivity and specificity of 0.681 and 0.691, respectively.

Multivariate Analysis

The results of the forward stepwise conditional logistic regression model using the seven significant variables as candidate variables indicate that the perceived inadequacy of personal protection equipment supply (adjusted OR = 4.27, 95% CI 1.66 to 12.54, $p = 0.0028$), SARS infection control training <2 hours or no training (adjusted OR = 13.6, 95% CI 1.24 to 27.50, $p = 0.002$), and inconsistent use of more than one type of personal protection equipment when having direct contact with SARS patients (adjusted OR = 5.06, 95% CI 1.91 to 598.92, $p = 0.02$) were significantly and independently associated with SARS infection among hospital workers.

Discussion

Breakthrough transmission was likely responsible for the SARS infection of these cases, as protective masks (primarily N95) were used consistently by almost all of the cases. All workers were required to wear protective masks from March 12, 2003. Using protective masks alone is, therefore, not sufficient to eliminate SARS transmission among hospital workers. Cases were less likely to have had direct contact with a SARS patient than controls, suggesting that direct physical contact with SARS patients was not necessary for breakthrough transmission to occur. It also suggests that modes of transmission other than droplets cannot be excluded. Consistent hand hygiene after contact with patients was almost universal and was not a significant factor predicting SARS transmission in our study, although hand hygiene appeared to be a risk factor in situations when there was no patient contact.

Data from all the three settings show that inconsistent use of gown, cap, and goggles were all very strongly associated with breakthrough transmissions. Personal protection equipment should be used consistently in all three settings. The high degree of collinearity in the use of the various types of personal protection equipment makes it difficult to ascertain which type of personal protection equipment is most important as a SARS countermeasure. Nevertheless, policy makers should be made aware that the supply of different types of personal protection equipment had often been seen as inadequate, and it is one of the very significant risk factors identified. The perception of inadequate supply was not verified by this study. These perceptions may reflect the actual situation or may be an inaccurate impression of the hospital workers. Caution is advised in interpreting these results. Nevertheless, at the time of the study, the media had reported frequent complaints about personal protection equipment supply shortages from hospital workers. The perception of inadequate personal protection equipment is likely to be associated with the personal protection equipment supply situation. Given the large differences in our results (OR > 5.0, $p < 0.001$), it is likely that personal protection equipment

Table 5: Percentage distribution of the number of problems encountered by the hospital worker[a]

No. of problems encountered[b]	Controls			Case-patients			Matched OR (exact 95% CI)	p value (exact)
	n	%	Cumulative %	n	%	Cumulative %		
0	27	20.1	20.1	1	1.4	1.4	1.00	
1	65	48.5	68.6	21	30.4	31.8	8.47(1.37 to ∞)	0.0169
2	24	17.9	86.5	17	24.6	56.4	17.78(2.67 to ∞)	0.0010
≥3[c,d]	18	13.4	100.0	30	43.5	100.0	44.15(7.02 to ∞)	<0.0001

[a]Excluded nine controls and thee cases that had at least one missing entry on one of the problems encountered.
[b]The seven problems are: 1) inconsistent use of at least 1 type of personal protection equipment when having contact with SARS patients, 2) with "patients in general," 3) when there was "no patient contact," 4) when SARS infection control training was less than 2 hours, 5) when the respondent reported not understanding SARS infection control procedures, 6) when at least one personal protection equipment was perceived to be in inadequate supply in the 3 settings, and 7) when hand hygiene was inconsistent when there was "no patient contact."
[c]Percentages of the number of problems encountered in the control group: 3 problems (6.7%), 4 problems (4.5%), 5 (1.5%), 6 (0.7%), and 7 (0%).
[d]Percentages of the number of problems encountered in the case group: 3 problems (10.1%), 4 (8.7%), 5 (13.0%), 6 (8.7%), and 7 (2.9%).

shortages were at least partially responsible for many of the SARS infections. As inadequate knowledge of SARS infection control ("did not understand procedures") is also a strong risk factor for breakthrough transmission, SARS infection control training must not be overlooked. In-depth, thorough training (≥2 hrs) is required.

Soon after the initial SARS outbreak, it was mandatory for all hospital workers to attend at least one 1-hour structured training session delivered by the infection control team, and the records of these sessions were collected and submitted to the Hospital Authority. These training sessions were conducted twice per day for the initial week from the middle of March and daily until the end of June. The content of these training sessions included basic knowledge of SARS and its clinical presentation, route of transmission, types and proper use of different personal protective equipment for different risk levels, the procedures for handling high risk specimens, environmental disinfection protocols, and commonly observed problems. The content of the training was regularly revised with updated information. Regular updates and attendance of the training sessions were strongly recommended. The unit supervisors were given more intensive training to train their staff. The findings of this study underscore the importance of in-depth training in SARS prevention among hospital workers.

The findings eliminate a number of speculated risk factors which include the following: performing particular high-risk procedures on SARS patients, having social contacts with people who were later found to have SARS cases, and experiencing various minor problems in using the mask. Performing high-risk procedures was not a significant factor, hence, it is speculated that this is due to a high degree of awareness and caution taken when performing these procedures with SARS patients.

It is found that those who encountered any of the seven identified problems had a greatly increased likelihood of contracting SARS. The number of problems encountered is a strong predictor of SARS infection. It is recommended that, after each day's work, health workers complete a checklist to be reviewed by management. No hospital staff should be exposed to SARS before receiving adequate training or before they have obtained a thorough understanding of the infection control procedures. The results of the multivariate analysis show that infection control training, personal protection equipment use, and perceived supply were independently associated with SARS infection risk among hospital workers.

This study has a number of limitations. As a case-control study, it is subject to recall bias. However, the recall period was usually within 1 week as all the case-patients were interviewed while they were hospitalized. Hand hygiene data were self-reported and not audited. Nevertheless, since respondents were required to report the frequency of hand washing from a categorical response format rather than an open ended question, the responses should be reasonably reliable. Another possible bias may be the case group's attributing their infection to external factors (e.g., inadequate supplies) and the control group's doing the opposite. Given that the odds ratios obtained were strongly significant and consistent with one another, it is unlikely that this form of bias could account for all of the observed differences. The study, however, has a relatively large sample size, a high response rate, and has controlled for the exposure to other background confounding factors.

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Possible SARS Coronavirus Transmission during Cardiopulmonary Resuscitation

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Infection of healthcare workers with the severe acute respiratory syndrome–associated coronavirus (SARS-CoV) is thought to occur primarily by either contact or large respiratory droplet transmission. However, infrequent healthcare worker infections occurred despite the use of contact and droplet precautions, particularly during certain aerosol-generating medical procedures. We investigated a possible cluster of SARS-CoV infections in healthcare workers who used contact and droplet precautions during attempted cardiopulmonary resuscitation of a SARS patient. Unlike previously reported instances of transmission during aerosol-generating procedures, the index case-patient was unresponsive, and the intubation procedure was performed quickly and without difficulty. However, before intubation, the patient was ventilated with a bag-valve-mask that may have contributed to aerosolization of SARS-CoV. On the basis of the results of this investigation and previous reports of SARS transmission during aerosol-generating procedures, a systematic approach to the problem is outlined, including the use of the following: 1) administrative controls, 2) environmental engineering controls, 3) personal protective equipment, and 4) quality control.

During the global spread of severe acute respiratory syndrome (SARS) (1–5), a great deal was discovered about the illness and the SARS-associated coronavirus (SARS-CoV) (6,7). SARS-CoV infection is thought to occur primarily by either contact or large respiratory droplet transmission (3,8). However, despite the use of infection control precautions and personal protective equipment designed to prevent contact and droplet transmission, episodes of SARS-CoV transmission to healthcare workers have continued to occur under certain circumstances.

Of particular concern are procedures performed on SARS patients that may aerosolize SARS-CoV and lead to limited airborne transmission or enhanced contact and droplet transmission (9). Such procedures include noninvasive positive pressure ventilation (BiPAP), intubation, and high-frequency oscillatory ventilation. As a result, special infection control procedures have been recommended for aerosol-generating procedures (10,11). We present the results of an investigation of the first reported transmission of SARS-CoV to healthcare workers that occurred during attempted cardiopulmonary resuscitation of a completely unresponsive SARS patient. On the basis of the results of this investigation, as well as previous reports of SARS transmission during aerosol-generating procedures, we used the continuous quality improvement framework (12) to suggest interventions for preventing future episodes of transmission.

Methods

Data were collected through interviews of healthcare workers present during the attempted cardiopulmonary resuscitation where transmission of SARS-CoV was thought to have occurred. Interviews included a structured questionnaire component. Hospital and provincial policies

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in place at the time of the resuscitation were reviewed. The hospital patient-care environment was inspected by a team of environmental engineers and industrial hygienists. Laboratory specimens, collected with nasopharyngeal swabs, were obtained from healthcare workers with symptoms that fulfilled the SARS clinical case definition after exposure during the attempted cardiopulmonary resuscitation. These were tested by reverse transcriptase–polymerase chain reaction (RT-PCR) with primers specific for SARS-CoV (7). After participants gave informed consent, convalescent-phase serum was collected from all consenting healthcare workers exposed to the attempted resuscitation event as part of a larger seroprevalence study of hospital staff. For this, samples were analyzed with a commercially available indirect immunofluorescent assay (Euroimmune, Lübeck, Germany) according to the directions of the manufacturer.

In addition, a limited evaluation of the Stryker T4 Personal Protection System (Stryker Instruments, Kalamazoo, MI), worn by some of the healthcare workers involved in the resuscitation attempt, was conducted to estimate the operating parameters, including particle removal efficiency and air-flow rate. A Met One Model 227B Hand-Held Particle Counter (Met One, Inc., Grants Pass, OR) was used to count ambient particles outside and inside the hood; five replicates were collected for each condition over a 1-minute sampling period. All information was obtained as part of an ongoing joint investigation into the cause of the second phase of the Toronto SARS outbreak conducted by Toronto Public Health, Health Canada, and the Centers for Disease Control and Prevention (13).

Case Report

A 67-year-old woman with a history of asthma was admitted to hospital A on May 24, 2003, with a 5 day history of fever, cough, malaise, headache, and myalgias. The patient's mother had recently been admitted to the same hospital and died of a nosocomial pneumonia after orthopedic surgery for a fractured hip. On the basis of clinical findings and the identification of secondary infections in exposed persons, the mother's death was retrospectively determined to be due to SARS. On admission, the patient was febrile and her chest radiograph showed left lower lobe and lingular infiltrates. Both acute-phase serologic tests and serum RT-PCR were positive for SARS-CoV (National Microbiology Laboratory, Health Canada, Toronto). She was admitted to the hospital and placed in respiratory isolation on the SARS unit. Progressive respiratory failure later developed in the patient, and within 72 hours of admission, she required 100% supplemental oxygen. On May 28, 2003, she was found to have no vital signs and cardiopulmonary resuscitation was attempted.

Nine healthcare workers participated in the resuscitation attempt. Three ward nurses (RN1–3) were the initial responders (Table). RN1 performed chest compressions while RN2 and RN3 prepared suction, oxygen, and intubation equipment. Three intensive care unit nurses (ICU-RN1–3), two respiratory therapists (RT1 and 2), and a physician (MD) also participated in the resuscitation. ICU-RN1 took over chest compressions from ward-RN1. ICU-RN2 inserted a peripheral intravenous catheter (IV) in the left foot of the patient and administered medications via the IV during the resuscitation attempt. ICU-RN3 ventilated the patient with a bag-valve-mask, without a bacterial/viral filter. RT1 performed the endotracheal intubation, which was completed in <30 seconds. No suctioning was required during or after the intubation and no respiratory secretions or other bodily substances were observed in the environment. A bacterial/viral filter was placed on the bag-valve-mask after the intubation.

All nurses in the room during the resuscitation were wearing protection equipment that was considered standard for routine SARS patient care at this hospital. This equipment consisted of two gowns, two sets of gloves, goggles, a full-face shield (with the exception of RN1 and RN2), shoe covers, hair cover, and NIOSH-approved N95 disposable respirators that were not fit-tested. In addition, all nurses involved in the resuscitation were experienced in working on SARS units and thus familiar with the recommended infection control policies and procedures. In contrast to the nurses, both RTs and the MD were wearing T4 Personal Protection Systems during the resuscitation. All nurses left the room immediately after the intubation and removed their protection equipment following the standard hospital protocol. Approximate exposure times are outlined in the Table.

On the May 31, 2003, both ICU-RN1 and ICU-RN2 had a temperature >38.0°C, myalgia, and malaise. In addition, ICU-RN1 complained of headache and nausea, and ICU-RN2 reported dyspnea. ICU-RN1 had a normal chest radiograph results, but the radiograph of ICU-RN2 showed a left lower lobe infiltrate that persisted for several days. Both RNs were admitted to the hospital for observation; their condition remained stable. RN3 reported a headache and myalgia on June 1, 2003, but her maximum temperature reached only 37.8°C. She remained in home quarantine, and her symptoms resolved without further progression. Results of RT-PCR performed on nasopharyngeal swabs from ICU-RN1 and ICU-RN2 were negative (7). At present, only one case (ICU-RN2) meets the World Health Organization criteria for probable SARS, one case (ICU-RN1) is under investigation, and the third (RN3) does not meet the case definition as her temperature remained <38.0°C (14). A review of the 48-hour period before the resuscitation did not show any other likely transmission

Table. Healthcare worker exposures, personal protective equipment, and outcome

Code team member	Tasks (duration of exposure)	Exposure time	Protective equipment	Symptoms (onset)	SARS serologic findings
Ward RN1	Contact before code (120 min), compressions (<5 min), assisted IV insertion (5 min), observed code (10 min), wrap body (10–15 min)	150–155 min	Gown x 2, gloves x 2, safety glasses, shoe covers, hair cover, N95 respirator	None	Refused testing
Ward RN2	Set up suction equip (5 min), charting arrest record (15 min), wrapped body (10–15 min)	30–35 min	Gown x 2, gloves x 2, safety glasses, face shield, shoe covers, hair cover, N95 respirator	None	Negative
Ward RN3	Set up oxygen equip (5 min), prepared intubation equipment (10 min), observed (5 min), wrapped body (10–15 min)	30–35 min	Gown x 2, gloves x 2, safety glasses, face shield, shoe cover, hair cover, N95 respirator	Headache, myalgia, Tmax 37.8°C (June 1)	Negative
ICU RN1	Chest compressions (10–15 min)	10–15 min	Gown x 2, gloves x 2, safety glasses, face shield, shoe cover, hair cover, N95 respirator	Headache, malaise, myalgia, nausea, Tmax 38.0°C (May 31)	Indeterminate
ICU RN2	IV insertion in foot (<5 min), medication administration (10 min), application of EKG leads (<1 min)	10–15 min	Gown x 2, gloves x 2, safety glasses, face shield, shoe cover, hair cover, N95 respirator	Myalgia, malaise, SOA, Tmax 38.5°C (May 31)	Positive
ICU RN3	Ventilated patient with bag-valve-mask (5–10 min)	5–10 min	Gown x 2, gloves x 2, safety glasses, face shield, shoe cover, hair cover, N95 respirator	None	Negative
RT1	Intubated patient (<30 s), ventilated patient with bag-valve-mask (10–15 min)	10–15 min	T4 Personal Protection System, N95 respirator	None	Refused testing
RT2	Put filter on ETT and assisted RT1 (5–7 min)	5–10 min	T4 Personal Protection System, N95 respirator	None	Refused testing
MD	Chest compressions (5–7 min)	5–10 min	T4 Personal Protection System, N95 respirator	None	Refused testing

[a]SARS, severe acute respiratory syndrome; RN1, ward nurse 1; RN2, ward nurse 2; RN3, ward nurse 3; ICU-RN1, intensive care unit nurse 1; ICU-RN2, intensive care unit nurse 2; ICU-RN3, intensive care unit nurse 3; RT1, respiratory therapist 1; RT2, respiratory therapist 2; MD, physician; IV, intravenous catheter; Tmax, maximum temperature; EKG, electrocardiogram; ETT, endotracheal tube

episodes. In particular, ICU-RN2 was the charge nurse in the ICU and had little or no direct patient contact in the 48 hours before the resuscitation. Five of the nine healthcare workers involved in the resuscitation agreed to participate in serologic testing. All convalescent-phase samples were collected >30 days after the event (Table).

Evaluation of the Stryker T4 Personal Protection System indicated an average removal efficiency of 68% for particles >0.5 μm in diameter and 54% for particles >5 μm. This equates to a reduction factor (i.e., particles outside of the hood would be reduced in number by this factor) of 3.1 and 2.2, respectively.

Discussion

This report describes the apparent transmission of SARS-CoV from a patient to healthcare workers during an attempted resuscitation. The similar symptom onset dates suggest a point source of exposure. In this case, SARS-CoV was transmitted despite healthcare workers' wearing protection equipment designed to protect against contact and droplet transmission; no breaches in droplet protection equipment were identified, and exposure times were fairly brief. Although SARS transmission that involved intubation and BiPAP (9) have been reported, this episode is unique in that the patient was neither conscious nor breathing at the time of the intubation, and the intubation procedure was performed quickly and without difficulty. These factors make it less likely that transmission occurred as a direct result of the intubation procedure. Instead, it is more likely that transmission was related to events leading up to the intubation. In this case, just as in previous cases, either contact, droplet, or airborne transmission might have occurred.

Direct and indirect contact are the most common forms of transmission for most nosocomial pathogens; transmission between patients or from patient to healthcare worker usually follows contamination of the healthcare workers' hands after touching either the patient or a fomite that came into direct contact with the patient. Large aerosol droplets (i.e., >10 μm) can, in addition to contaminating both animate and inanimate surfaces in close range of the patient, travel short distances through the air and make direct contact with the exposed mucous membranes of healthcare workers or other patients.

In contrast, airborne transmission is mediated by respiratory aerosols. These aerosols of infectious organisms contain droplet nuclei <10 μm in size and, depending upon their size within this range as well as ambient environmental

conditions, can float on air currents and remain airborne for many hours (15–18). A large variety of viruses (16,19–27) are transmissible through both contact and airborne modes. Often, investigation of the epidemiology of nosocomial viral infections, establishes the occurrence of airborne transmission (15).

Two explanations may account for the transmission observed in this case: 1) an unrecognized breach in contact and droplet precautions occurred, or 2) an airborne viral load was great enough to overwhelm the protection offered by droplet precautions, including non–fit-tested N95 disposable respirators. If the last form of transmission was responsible, airborne virus may have been generated by the coughing patient (16) before her cardiopulmonary arrest or due to a "cough-like" force produced by the airway pressures created during asynchronous chest compressions and ventilations using the bag-valve-mask (28).

Regardless of the exact mode of transmission in this case, several lessons were learned through our investigation that may help reduce the risk of transmission to healthcare workers. A systematic approach to this problem is outlined considering the following framework: 1) administrative controls, 2) environmental engineering, 3) protection equipment, and 4) quality control.

Administrative Controls

Policies and protocols for emergency resuscitation involving patients known to have or suspected of having SARS should include 1) description of the roles and responsibilities of healthcare workers responding to the emergency, 2) mechanisms to alert responders that the emergency involves a potentially contagious patient (e.g., announcing the code as an "isolation code blue"), 3) steps to limit the number of healthcare workers involved to minimize potential exposures, 4) plans for having auxiliary staff staged in a safe area where they can be easily called on if needed but otherwise preventing unnecessary exposure, 5) plans for safe disposal and cleaning of equipment used during the emergency response, and 6) procedures for disposition of the patient after the emergency, either to the ICU if resuscitation is successful or the morgue if unsuccessful.

Policies must be developed that consider all high-risk exposures or emergency situations and not just individual procedures. Policies that are too focused are of little value in dealing with the hundreds of unforeseeable possible situations that may arise. Conversely, policies that educate healthcare workers to assess the risks of a task and empower them to take appropriate protective action will be more effective. These policies should be crafted at each healthcare facility by a team that involves key stakeholders, including persons involved in the clinical response along with infection control practitioners and infectious disease experts.

It is also important to minimize the chance that a patient will suffer unwitnessed cardiopulmonary arrest or require emergency intubation on a SARS unit. Prevention of these events will involve two changes in policy. The first is to recognize that isolation wards cannot be staffed with the same nurse-to-patient ratio as a regular ward. Care of patients in isolation is more time intensive due to both the physical barriers (e.g., anterooms, doors kept closed at all times) and the required use of protection equipment. The nurse-to-patient ratio on the SARS ward at the time of the arrest was between 1:4 and 1:5; a more ideal ratio might be 1:2 or 1:3. It is also necessary to have a lower threshold for transferring patients to a higher acuity setting (i.e., ICU or stepdown unit) when they first begin to show signs of a clinical deterioration. To enable this, all patients on a SARS unit should have measurement of vital signs along with pulse oximetry at a minimum of every 4 hours. Should their oxygen saturation drop below 92% on room air one should administer oxygen through nasal prongs 1–4 L per minute to maintain saturation >92%, and increase vital signs/pulse oximetry to every 2 hours. If the patient subsequently requires oxygen through nasal prongs at >4 L per minute the responsible physician should be notified and increase vital signs or pulse oximetry to every 1 hour. Finally, if the patient requires supplemental oxygen of >40% to maintain saturation >92%, the patient should be transferred to the intensive care unit and undergo elective intubation in a controlled manner. This later policy has worked well in other SARS units, as well as in hospital A after it was implemented by one of the authors (M.L.) after this cluster.

Finally, policies should be developed to address the appropriateness and application of advanced cardiac life support for patients suffering cardiopulmonary arrest on a SARS ward. Many considerations must enter into any such discussion, including the usefulness and outcome of resuscitation efforts, particularly in unwitnessed arrests (29–31). Despite even the most well-planned and well-written policies, if healthcare workers are not trained in proper infection control practices, SARS will continue to be transmitted. Staff must be trained in both the application of policies as well as the use of protection equipment. In addition to education, practice is also important; for example, consideration should be given to staging one or more "mock SARS code blue" events.

Environmental Controls

The second line of defense against the transmission of SARS is environmental engineering controls. These consist of physical engineering elements such as negative pressure rooms, dilution ventilation, high-efficiency particulate air filtration, ultraviolet lights, and scavenging devices. The primary goal of environmental engineering

processes is to contain the infectious agent in a limited area and to minimize or rapidly decrease the viral load in the environment so that in the event of a breach in infection control process or protection equipment, the chance of healthcare workers or other patients becoming infected is minimized. In this case, a breach occurred in source control; the initial bag-valve-mask used in the resuscitation did not have a viral/bacterial filter on the exhaust. This breach may have resulted in "uncontrolled" release of aerosolized virus into the environment. However, previous studies with coxsackie virus showed that little or no virus is detectable in expired air, only in respiratory aerosols and droplets from coughing or sneezing (16,21).

Personal Protective Equipment

The final line of protection against occupational exposure is protection equipment. The use of N95 respirators offers a level of protection against airborne transmission of SARS. However, for any form of respiratory protection to perform at the level of its full potential, it must be properly fitted to provide an adequate seal. The N95 disposable respirators used by healthcare workers in this instance were not fit-tested to ensure an adequate seal. Thus the exact level of protection afforded by the N95 respirators for each person in this case is unknown. Nonetheless, a higher level of respiratory protection should be considered in environments with a potentially very high SARS-CoV load, such as that associated with aerosol-generating procedures

As a result of the transmission of SARS Co-V during aerosol-generating procedures, some hospitals in Ontario, Canada, have adopted use of the T4 Personal Protective System (Stryker Instruments) (Figure 1). This system was originally designed to maintain a highly sterile field during surgery to prevent operative site infections.

As a form of protection equipment, this system has both advantages and disadvantages. The primary advantage is that the entire body of the healthcare worker is covered, providing a high level of droplet protection. The primary disadvantage of the T4 is the length of time required to put one on during an emergency. In the emergency resuscitation described in this report, the delay in certain rescuers responding was due to the time required to put on the T4. This resulted in the need for a second code blue to be announced for the same patient, which drew additional personnel to the code and thus increased the number of healthcare workers exposed to SARS.

The healthcare worker must also be attentive to avoid contamination when removing the T4. Moreover, the airborne reduction factors of 3.1, for particles >0.5 μm in diameter, and 2.2 for particles >5 μm were less than the protection factor of 10 that is assigned (i.e., minimum expected in practice) for a fit-tested, disposable N95 respirator. However, a disposable N95 is commonly worn under the T4 used in Ontario hospitals, suggesting the respiratory protection afforded healthcare workers using the T4 would be greater.

The powered air-purifying respirators (PAPRs) most commonly used in healthcare settings have a disposable full hood with face shield covering the healthcare worker's upper body (Figure 2). This device provides a higher level of protection against airborne infectious agents (any PAPR equipped with a hood or helmet with any type of particulate air filter has an assigned protection factor of 25 [32]), and it may be faster and easier to apply in an emergency situation. Finally, ensuring that a hospital has adequate

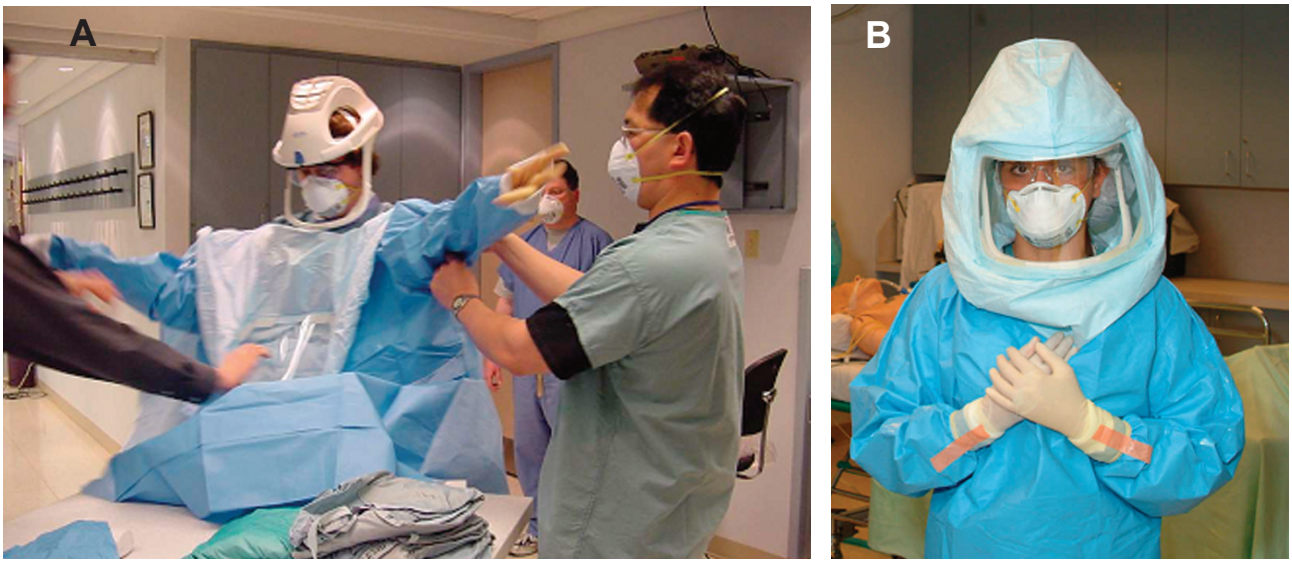

Figure 1. A, T4 Stryker suit being applied with aid of assistants. B, Healthcare worker in T4 Stryker suit. Photos provided by Randy Wax and Laurie Mazrik, Ontario Provincial SARS Biohazard Education Team.

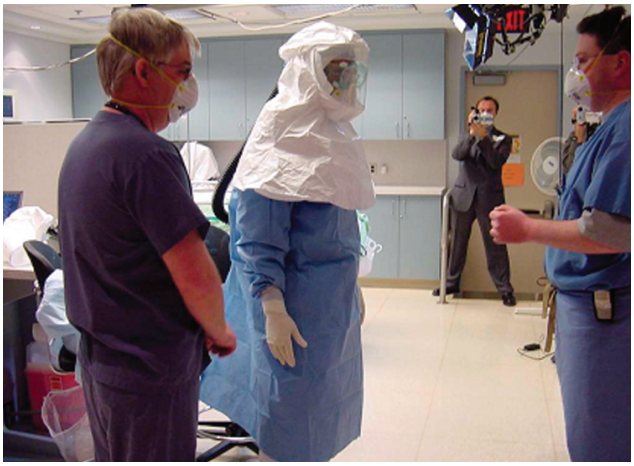

Figure 2. Healthcare worker wearing powered air-purifying respirators for demonstration. Photos provided by Randy Wax and Laurie Mazrik, Ontario Provincial SARS Biohazard Education Team.

protection against airborne diseases, even if not absolutely required for SARS, will ensure that staff are prepared to deal with future emerging infectious diseases or bioterrorism events that could involve airborne agents.

Regardless of what device (T4 versus PAPR) is used in an institution for potentially aerosol generating procedures, it is essential that they are distributed throughout the hospital in areas where they are most likely to be required by primary responders in an emergency situation as opposed to a central area where teams must wait for them to be brought to the emergency. In addition, extra protection equipment should be included as part of any "crash cart" used by the responding code team.

Quality Control

Although there is a tendency to focus only on high-tech forms of protection equipment, it is important not to forget the basics of infection control procedures such as glove changing and hand hygiene. Healthcare workers must remain vigilant about not only protecting themselves from SARS transmission but also protecting against patient-to-patient transmission. As was found in the second phase of the SARS outbreak in Toronto (13), one of the best ways to prevent healthcare worker infections is to ensure that no sustained transmission of SARS occurs within the patient population, which may act as a reservoir of infection.

After developing good policies and training staff who are rehearsed for emergencies and provided with appropriate protection equipment, the last step is to ensure ongoing adherence to the standards set. This adherence is achieved through quality control. Without an effective quality control program in place, lapses in infection control procedures will occur, particularly as healthcare workers become fatigued during a prolonged outbreak.

A variety of quality control methods can be implemented, including administrative checks to ensure equipment is in good repair, policies are current, and training materials are up to date. Another quality control practice often used by emergency services personnel dealing with hazardous situations is the "buddy system." In this system, healthcare workers always work in teams on SARS units with each person being responsible for double checking to make sure that their partner is wearing appropriate equipment and following correct infection control practices before entering a patient's room. Finally, a process should be in place to review responses to emergencies after they have occurred to learn from the experience and facilitate continuous quality improvement.

Conclusion

SARS has increased the medical community's awareness of issues related to occupational health and safety. It has also highlighted the importance of infection control programs and practices. A systematic approach, including administrative controls, environmental engineering, protection equipment, and quality control, is advocated to prevent future SARS-CoV transmission to healthcare workers.

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Detection of SARS Coronavirus in Patients with Suspected SARS

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Cases of severe acute respiratory syndrome (SARS) were investigated for SARS coronavirus (SARS-CoV) through RNA tests, serologic response, and viral culture. Of 537 specimens from patients in whom SARS was clinically diagnosed, 332 (60%) had SARS-CoV RNA in one or more clinical specimens, compared with 1 (0.3%) of 332 samples from controls. Of 417 patients with clinical SARS from whom paired serum samples were available, 92% had an antibody response. Rates of viral RNA positivity increased progressively and peaked at day 11 after onset of illness. Although viral RNA remained detectable in respiratory secretions and stool and urine specimens for >30 days in some patients, virus could not be cultured after week 3 of illness. Nasopharyngeal aspirates, throat swabs, or sputum samples were the most useful clinical specimens in the first 5 days of illness, but later in the illness viral RNA could be detected more readily in stool specimens.

In early 2003, severe acute respiratory syndrome (SARS) was recognized as a newly emerging pneumonic disease (1–3). A proportion of patients have watery diarrhea, usually at a later stage of the illness, suggesting that the infection may not be confined to the respiratory tract (4). A novel coronavirus, designated as SARS coronavirus (SARS-CoV), was implicated as the causative agent (5–7), and the respiratory disease has been reproduced in a nonprimate animal model (8). Hong Kong was one of the regions most affected, with >1,700 patients. Specific laboratory tests to detect viral RNA and antibody responses (5) were used to establish a cause in patients suspected to have SARS. Although virologic results for small cohorts of patients have been reported (4,5,9), analysis of results of these first-generation tests in routine clinical practice has not been published previously. We report the correlation of results of reverse transcriptase polymerase chain reaction (RT-PCR) and immunofluorescent serologic testing for SARS-CoV in 1,048 cases investigated for SARS in the first 5 weeks after the first-generation diagnostic tests became available in Hong Kong.

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Methods

Patients

In the weeks after the first-generation viral diagnostic tests became available in Hong Kong, SARS-CoV diagnosis was carried out in three laboratories, one of which was the Department of Microbiology of Queen Mary Hospital (QMH). Results from specimens investigated at QMH laboratory from April 1 through May 3, 2003, and subsequent follow-up specimens are included in this analysis. Clinical specimens used for viral RNA detection included nasopharyngeal aspirates, throat and nose swabs, saliva, sputum, endotracheal aspirates, feces, and urine. Nasopharyngeal aspirates were collected into a mucus trap, and residual secretions in the catheter were sucked into the trap by aspirating 2 mL of virus transport medium. Swabs were collected into 2 mL of virus transport medium containing vancomycin (final concentration 100 μg/mL), amikacin (30 μg/mL), and nystatin (40 U/mL). Urine and feces were collected into specimen containers and submitted directly to the laboratory without the addition of transport medium.

The case definition has been previously described (5,10). Patients were categorized on a clinical basis as "clinical SARS," "suspected SARS," and "not SARS" by the attending clinicians, depending on the response to antimicrobial therapy for bacterial pathogens (e.g., tazocin 2.25–4.5 g intravenously 6–8 h/d, or azithromycin 500 mg/d for 7–10/d), the clinical and radiologic evolution of the illness, history of contact with other patients with SARS, and an alternative diagnosis that fully explained the clinical findings.

Fecal, throat swab, and serum specimens from controls were obtained for comparison. Fecal specimens from patients with diarrhea were anonymously tested for SARS-CoV RNA. Throat swab specimens were collected after informed consent from patients attending primary care

facilities for nonrespiratory diseases and tested for SARS-CoV RNA. Blood donor sera left over from screening for bloodborne viruses were tested anonymously for antibodies to SARS-CoV.

Viral RNA Detection

RNA extraction was performed by using QIAamp Viral RNA kit reagents (Qiagen, Hilden, Germany) according to the manufacturer's instructions. The RT-PCR primers and conditions have been described (5,11). Since these primers gave occasional false-positive reactions with stool specimens, all PCR-positive stool specimens were retested by the LightCycler PCR (Roche Diagnostics GmbH, Mannheim, Germany) for confirmation using the same two sets of primers, with the melting curve analysis being used to provide additional confirmation of reaction specificity (9). A plasmid vector pCRII-TOPO (Invitrogen, San Diego, CA) containing the RNA-dependent RNA polymerase-encoding sequence of the virus was used as the reference standard. A series of five $\log_{10}$ dilutions corresponding to 1 x 10^1 to 1 x 10^6 copies per reaction of reference standard was run in parallel with the test samples.

Virus Isolation

Specimens resuspended in virus transport medium (200 µL) were used for infecting fetal rhesus monkey kidney (FRhK-4) cell monolayers in culture tubes. Approximately 1 g of feces samples was resuspended in 10 mL virus transport medium and centrifuged, and the supernatant was spread onto cells. The respiratory samples were already diluted in virus transport medium and spread onto the cell monolayer. After incubation at 37°C for 1 h, the cells were fed with 1 mL of minimum essential medium with 1% fetal calf serum (GibcoBRL, Grand Island, NY) and incubated at 37°C. The cultures were examined for cytopathic effect (CPE) each day for 14 days. At the end of the incubation period or when CPE appeared, the cells were spotted on Teflon-coated slides, fixed with ice-cold acetone, and stained for SARS-CoV antigen by using a convalescent-phase human serum. The identification of the isolate was confirmed by RT-PCR.

Serologic Testing

Coronavirus immunoglobulin G serologic testing was performed by indirect immunofluorescence. Batches of SARS-CoV–infected Vero cell smears were prepared and fixed in ice-cold acetone for 10 minutes. The cells were adjusted to be 60% to 70% SARS-CoV infected, as judged by immunofluorescent staining with a control positive human convalescent-phase serum. The fixed smears were stored at –70°C until use. Serum samples were screened at a dilution of 1:10 on infected and uninfected control cells. After 30 minutes of incubation, the cells were washed twice in phosphate-buffered saline (PBS) for 5 minutes each, and then goat anti-human fluorescein isothiocyanate conjugate (INOVA Diagnostics, Inc., San Diego, CA) was added, and the cells were incubated for 30 minutes at 37°C. The cells were washed again as described and examined with an immunofluorescent microscope. Serum samples positive at a screening dilution of 1:10 were titrated with serial twofold dilutions in parallel with the respective acute-phase serum specimen from the same patient. A positive control serum was tested with each batch of cells.

Biosafety

Virus isolation or preparing cell smears for serologic testing was done in a biosafety level (BSL) 3 laboratory. Routine handling of clinical specimens for RNA extraction and serologic testing by immunofluorescence were done in a BSL-2 laboratory. Basic laboratory practice was reinforced by educating staff and closely supervising work practices. Serum specimens for antibody testing were heat inactivated at 56°C for 30 minutes before testing.

Results

The sensitivity and specificity of the RT-PCR and the real time LightCycler assays have been reported (9,11,12). A total of 3,611 respiratory, fecal, and urine specimens and 1,699 serum samples were tested for SARS-CoV RNA and antibody, respectively, from 1,048 patients for whom an initial clinical suspicion of SARS was considered. The laboratory results were retrospectively correlated with the clinical diagnoses of these patients. Clinically, 590 of these patients were considered to have clinical SARS, 79 to have suspected SARS, and 379 not to have SARS. The third group included patients hospitalized with febrile respiratory illnesses, many with radiologic changes, in whom SARS had been initially considered in the differential diagnosis.

Overall, 948 (91%) of the patients had one or more specimens tested for SARS-CoV RNA by RT-PCR, and 454 (43%) had acute- and convalescent-phase serum samples available for serologic analysis, with a convalescent-phase serum taken at least 21 days after onset of illness. While specimens for RT-PCR were available from similar proportions (89%–91%) of patients in each clinical category, paired sera were more frequently available from patients clinically categorized as having SARS (417 [71%] from 590) than from patients in the not SARS category (25 [7%] from 379) (Table 1).

Of the patients clinically diagnosed as having SARS, 322 (60%) of 537 patients had evidence of SARS-CoV RNA in clinical specimens. In contrast, 2 (0.6%) of 341 of those clinically diagnosed as the "not SARS" category had RT-PCR evidence of SARS-CoV infection (Table 1). To assess the extent of circulation of SARS-CoV in the gener-

Table 1. SARS-CoV RNA detection by RT-PCR in clinical specimens[a]

Category	Patients tested	Patients positive (%)
Clinical		
Clinical SARS (n = 590)	537	322 (60.0)
Suspected SARS (n = 79)	70	1 (1.4)
Non-SARS febrile respiratory illnesses (n = 379)	341	2 (0.6)
Hospital controls		
Cohort 1: fecal samples from non-SARS patients with diarrhea	184	1 (0.5)
Community controls		
Cohort 2: throat swabs from patients with nonrespiratory illness visiting community physicians.	148	0 (0.0)

[a]SARS, severe acute respiratory syndrome; SARS-CoV, severe acute respiratory syndrome coronavirus; RT-PCR, reverse transcriptase–polymerase chain reaction.

al population, 184 fecal specimens (submitted for investigation of diarrheal illnesses from patients thought not to have SARS) and 148 nose and throat swabs (from patients visiting a general practice for nonrespiratory illnesses) were tested for viral RNA by RT-PCR. None of 148 control throat swab specimens and 1 of 184 control stool specimens had evidence of detectable SARS-CoV RNA.

Of 417 patients with clinical SARS for whom paired sera were available, 383 (92%) had a ≥4-fold rise in antibody titer to SARS-CoV. None of 45 controls had seroconversion to SARS-CoV. Two (8%) of 25 patients clinically diagnosed as the "not SARS" category seroconverted (Table 2), but a further 47 convalescent-phase sera from patients in this group failed to show any more seropositive patients (data not shown). Neither of these two patients had a history of contact with other patients with SARS. However, one had a left mid-zone consolidation confirmed by high-resolution computed tomography scan and had a discharge diagnosis of pneumonia of unknown cause. The other had a mild febrile illness of unknown cause without radiologic evidence of consolidation. None of 200 blood donor serum samples collected in Hong Kong during March 2003 and 2,200 additional serum samples collected in May 2003 had evidence of antibody to SARS.

The profile of SARS-CoV RNA detection in the 386 patients with serologically confirmed SARS-CoV infection was analyzed (Figure). Viral RNA was detectable in the respiratory tract of a proportion (11%–42%) of patients within the first 4 days of illness but was not detectable in stool or urine specimens until days 5 and 7 of the illness, respectively. The proportion of respiratory and stool specimens positive for viral RNA progressively increased and then peaked at approximately day 11 of the illness. While the nasopharyngeal aspirates and throat and nose swabs were the most productive specimens in the first 4 days of disease, stool samples were more useful after the 5th day of illness. Although the rate of detection in clinical specimens gradually decreased from day 16 onward, viral RNA could still be detected after 30 days of illness in samples from the nasopharynx, feces, and urine in a small proportion of patients (Figure). Smaller numbers of saliva, endotracheal aspirate, and sputum specimens were available for testing (Table 3).

Since confirmation of a laboratory diagnosis of SARS within the first 5 days of illness is the greatest clinical need, we studied the diagnostic yield from different specimens in patients with serologically confirmed SARS-CoV infection during this period (Table 4). Sputum appeared to be a good clinical specimen in the early stage of the disease, although the number of specimens tested was small. Nasopharyngeal aspirates and throat and nose swabs appear to be of comparable sensitivity (30% and 28%, respectively), while stool specimens are less useful specimens in the first 5 days of illness (sensitivity 20%). Saliva and endotracheal aspirates are alternative specimens (Table 3), but we could not assess their usefulness because of the lack of specimens collected in the early stage of the illness. In patients whose first specimen tested negative, 25 had a second specimen (of any type) collected within the first 5 days of illness. Three of these 25 were positive; the additional diagnostic yield from a second specimen was approximately 12% (data not shown).

Virus was isolated retrospectively from stored clinical specimens that were RT-PCR positive for viral RNA (Table 5). Virus was more readily isolated from the respiratory tract than from stool specimens. Furthermore, virus isolation was most successful during the first 2 weeks of the illness and was generally negative after day 22 of illness, even though virus was detectable in these specimens by RT-PCR.

Discussion

In April 2003, the first-generation diagnostic tests for the SARS-CoV became available to clinicians caring for

Table 2. Serologic response to SARS coronavirus[a]

Clinical category	No. of patients	Paired sera available for study	No. (%) of patients with fourfold rise in antibody titer to SARS-CoV
Clinical SARS	590	417	384 (92.1)
Suspected SARS	79	11	1 (9.1)
Not SARS	379	25	2 (8.0)
Controls	45	45	0 (0.0)

[a]SARS, severe acute respiratory syndrome; SARS-CoV, severe acute respiratory syndrome coronavirus.
[b]An additional 47 convalescent-phase sera were subsequently tested without any further evidence of antibody to SARS-CoV.

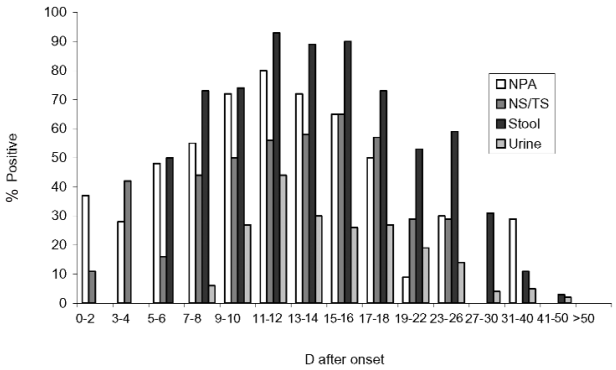

Figure. Reverse transcriptase–polymerase chain reaction percent positive in nasopharyngeal aspirates, nose and throat swabs, and stool and urine specimens at different days after onset of illness in patients with serologically confirmed severe acute respiratory syndrome. NPA, nasopharyngeal aspirate; NS/TS, nasal and throat swabs.

patients in whom SARS was considered in the differential diagnosis. Normally, new laboratory diagnostic tests are extensively evaluated and validated before they are introduced in routine clinical practice. However, in the case of SARS, a new and poorly understood disease, these first-generation test results were provided to clinicians on the understanding that the tests had not been validated and results had to be interpreted with caution.

Continued improvement of the sensitivity of RT-PCR methods (12) makes an analysis of the sensitivity of these first-generation diagnostic methods less relevant. However, these results provide useful information on the best specimens for detection of virus at different stages of illness, the tissue tropism of the virus, and the duration of virus excretion.

Culture of SARS-CoV for preparing the virus-infected cell smears and for virus isolation was carried out under BSL3 conditions, but routine clinical specimens were processed in the clinical virology laboratory under BSL2 conditions after enhanced and reinforced education on safety and good laboratory practice. Given that up to 250 specimens per day were being processed for RT-PCR detection and serologic testing during peak periods, the workload could not be managed in a BSL3 laboratory. None of the laboratory staff became ill with SARS symptoms, indicating that clinical specimens for serologic testing and RT-PCR can be processed safely in BSL2 level conditions.

The association of SARS-CoV with the clinical syndrome of SARS is illustrated by the detection rates of viral RNA in clinical specimens (60% in patients with SARS, 0.6% in the non-SARS group, and 0.3% of controls). Viral RNA detection by these first-generation RT-PCR tests is less sensitive than serologic testing for diagnosing SARS. Correspondingly, 92% of 417 patients with clinically diagnosed SARS and none of the paired sera from 45 unrelated controls seroconverted to SARS-CoV. However, 2 of 25 patients designated as "not SARS" category from whom paired sera were available also seroconverted. Paired sera were available from only a few (25 of 379) patients in the "not SARS" group. At a time of intense pressure on the clinical front-line staff, there was little incentive to obtain convalescent-phase sera from patients believed not to have SARS. These 25 patients may represent a biased sample of the larger group of non-SARS patients. This contention is supported by the fact that a further 47 convalescent-phase sera subsequently obtained from this group of "not SARS" patients failed to show any additional antibodies to SARS. Even patients in the "not SARS" category had a febrile, respiratory, often pneumonic, illness; one of the two patients in the "not SARS" category who had evidence of seroconversion had an undiagnosed pneumonic illness, while the other had an undiagnosed febrile illness without radiologic consolidation of the lung. Overall, a clinical diagnosis of SARS is closely correlated with detection of viral RNA by RT-PCR and seroconversion supporting the etiologic association of SARS-CoV and SARS.

None of 2,400 blood donor sera collected in Hong Kong during the height of the SARS outbreak has any evidence of antibody to the virus. This finding suggests that the spread of SARS-CoV infection in the general community was minimal, with most of the infection associated with clusters and hospital outbreaks (13).

The RT-PCR detection rates for SARS-CoV in respiratory, stool, and urine specimens in the 383 patients with seroconversion to SARS-CoV show that viral shedding

Table 3. SARS coronavirus RNA detection in saliva, endotracheal aspirates, and sputum at different times after onset of illness in patients with serologically confirmed SARS-CoV infection[a]

D after onset	Positive saliva samples/total (%)	Positive endotracheal aspirate/total (%)	Positive sputum/total
0–4	ND	ND	3/6
5–10	1/6 (17.0)	1/2	3/3
11–20	6/45 (13.3)	2/3	1/1
21–30	2/96 (2.1)	13/19 (68.4)	ND
31–40	3/58 (5.2)	1/1	ND
41–50	1/29 (3.4)	ND	ND
>50	0/40 (0.0)	0/1	0/1

[a]SARS, severe acute respiratory syndrome; SARS-CoV, severe acute respiratory syndrome coronavirus; ND, not done.

Table 4. RT-PCR for diagnosis of SARS-CoV in the first 5 days of illness in patients with serologically confirmed SARS-CoV infection[a]

Specimens evaluated	Positive/tested (%)
Nasopharyngeal aspirate	29/98 (29.6)
Swabs (throat, nose)	15/53 (28.3)
Sputum	5/9 (55.6)
Stool	5/25 (20.0)
Urine	0/15 (0.0)

[a]SARS, severe acute respiratory syndrome; SARS-CoV, severe acute respiratory syndrome coronavirus; RT-PCR, reverse transcriptase–polymerase chain reaction.

progressively increased from onset of the illness until approximately day 11 after onset. Since the first-generation RT-PCR test has relatively low sensitivity, these results reflect the increasing viral load at different clinical sites during the illness. Whereas these data are cross-sectional, in a previous study viral load in nasopharyngeal aspirates was followed up longitudinally in nasopharyngeal specimens collected at days 5, 10, and 15 after illness onset; results of this study also indicated that viral load peaks at day 10 of illness (4). Such a profile of a progressive increase in viral load is unusual for respiratory viral infections. Most other infections (e.g., respiratory syncytial virus, influenza) have peak viral titers in the respiratory secretions at or soon after the onset of clinical illness, after which viral titers and laboratory diagnostic yield decrease progressively (14). This "crescendo" pattern in SARS-CoV detection rates and viral load in clinical specimens has a number of implications. The pattern explains the poor sensitivity of the first-generation diagnostic tests during the first 5 days of the illness and emphasizes the challenge in making laboratory diagnosis early in the disease. These results may also suggest a fundamental difference in the efficacy of the innate immune response in controlling SARS-CoV infection, in contrast, for example, with influenza infection. Innate immune mechanisms are the earliest host defenses that control viral replication and, in the case of many respiratory viruses, do so within the first few days of illness, even before the specific adaptive immune responses have been activated. This response does not appear to occur with SARS, and viral load in the respiratory tract (4) begins to fall only when the antibody response appears, i.e., at approximately day 10 after onset of illness (4,5). This finding may suggest that SARS-CoV is able to evade the host innate response and requires the adaptive immune response to bring the infection under control. Finally, the peak viral load in the 2nd week of illness would predict that virus is more likely to be transmitted later in the course of the illness. This result indeed accords with epidemiologic observations (15). With regard to observations of viral load, the frequent use of steroid therapy in hospitals (16) is a confounding factor that may contribute to the increase in virus load later in the illness.

The relative virus detection rates from different specimens during the illness suggests that respiratory specimens (nasopharyngeal aspirate, throat swab) are more useful in the first 4 days of the illness, while fecal samples are better later in the illness. Urine samples, on the other hand, are not useful at any stage of the illness. A productive cough is not common in the early stage of illness, but in patients who do produce sputum, this specimen provides a high diagnostic yield. Thus, nasopharyngeal aspirates, throat swabs, and sputum, if available, are the best specimens in the first 5 days of the illness.

Detecting virus in the fecal and urine samples, in addition to the respiratory tract, suggests that SARS is not restricted to the respiratory tract. The finding of diarrhea unrelated to antimicrobial drug use in a number of patients supports evidence that the disease is not a purely respiratory one (4). A number of animal coronaviruses (e.g., mouse hepatitis virus and feline coronavirus) have tropism for multiple organs (17). Viral shedding is detectable by RT-PCR in the respiratory, gastrointestinal, and urinary tracts for many weeks after onset of illness, reflecting continued virus replication at these sites. However, SARS-CoV cannot be readily cultured from any of these sites after week 3 of illness. The viral RNA detected by RT-PCR after week 3 of illness is unlikely to represent persistence of viral RNA in the absence of ongoing viral replication. The apparent dissociation between virus isolation and RT-PCR may reflect the mucosal antibody's neutralizing the virus and rendering it less infectious. This observation also accords with the apparent absence of transmission of infection after week 2 of illness. The fact that virus isolation was done retrospectively may have affected the overall

Table 5. Virus isolation from specimens positive for SARS-CoV by RT-PCR[a]

	Sample type				
Wk	Positive NPA/sputum/total (%)	Positive TS/total (%)	Positive stool/total (%)	Positive urine/total (%)	Total pos/total tested (%)
1	3/11 (27.3)	0/3 (0)	0/0 (0)	0/0 (0)	3/14 (21.4)
2	20/37 (54.1)	1/6 (16.7)	0/11 (0)	1/4 (25.0)	22/58 (37.9)
3	0/6 (0)	1/6 (16.7)	1/18 (5.6)	0/0 (0)	2/30 (6.7)
4	0/3 (0)	0/0 (0)	0/7 (0)	0/0 (0)	0/10 (0)
Total	23/57 (40.4)	2/15 (13.3)	1/26 (3.8)	1/4 (25.0)	27/112 (24.1)

[a]SARS, severe acute respiratory syndrome; SARS-CoV, severe acute respiratory syndrome coronavirus; RT-PCR, reverse transcriptase–polymerase chain reaction; NPA, nasopharyngeal aspirate; TS, throat swab.

isolation rate. However, SARS-CoV appears relatively stable to freezing and thawing and is stable for many weeks in clinical specimens at 4°C or frozen at –70°C (K.H. Chan and J.S.M. Peiris, unpub. data). In any event, such a bias would be expected to be uniform both early and late in the disease.

In summary, SARS is closely associated epidemiologically with the novel SARS-CoV. The unusual profile of viral shedding from the respiratory tract may explain some of the observed transmission pattern of this disease, including the predilection for affecting healthcare workers.

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Real-Time Polymerase Chain Reaction for Detecting SARS Coronavirus, Beijing, 2003

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During the 2003 severe acute respiratory syndrome (SARS) outbreak, a real-time quantitative polymerase chain reaction, which targets the nucleocapsid gene at the 3' end of the viral genome, was established to detect and identify the SARS-associated coronavirus. We describe the use of this assay to screen >700 clinical samples.

Severe acute respiratory syndrome (SARS) is a new infectious disease of humans, first recognized in late February 2003 in Hanoi, Vietnam. The disease spread rapidly, with cases reported from 29 countries on five continents over 4 months (1–7). By July 3, 2003, this epidemic resulted in 8,439 reported cases globally, of which 812 were fatal (8). Rapid identification of the causal agent as a novel coronavirus (SARS-CoV) represents an extraordinary achievement in the history of global health and helped to contain the epidemic (7). Nonetheless, the epidemiology and pathogenesis of SARS remain poorly understood, and definitive diagnostic tests or specific treatments are not established. Since the origin of the virus and its animal reservoirs remain to be defined, the potential for recurrence is unknown. This fact underscores the importance of establishing sensitive and efficient methods for diagnosis and surveillance.

Immunofluorescence and enzyme-linked immunosorbent assays (ELISA) are reported to inconsistently detect antibodies to SARS-CoV before day 10 or 20 after the onset of symptoms, respectively (7,9). Thus, although helpful in tracking the course of infection at the population level, these serologic tools have less usefulness in detecting infection at early stages, when there may be potential to implement therapeutic interventions or measures, such as quarantine that may reduce the risk for transmission to naïve persons. In contrast, polymerase chain reaction (PCR)–based assays have the potential to detect infection at earlier time points. We describe a sensitive real-time PCR assay that can be readily standardized across laboratories and report its use in a survey of more than 700 samples from persons diagnosed with probable SARS during the 2003 epidemic in Beijing.

The Study

Primers and probe were selected in the N (nucleocapsid protein) gene region at the 3′ end of the SARS-CoV genome by using Primer Express Software (PE Applied Biosystems, Foster City, CA). The primer set used was: Taq-772F 5′-AAGCCTCGCCAAAAACGTAC (forward) and Taq-1000R 5′-AAGTCAGCCATGTTCCCGAA (reverse), Taq-955T 5′-FAM-TCACGCATTGGCATG-GAAGTCACAC-T-TAMRA (probe), labeled with the reporter FAM (6-carboxyfluorescein) and the quencher TAMRA (6-carboxytetramethylrhodamine) (TIB Molbiol, Berlin, Germany).

A calibration standard was generated by PCR amplification of a 1,277-bp fragment comprising part of the N open reading frame (ORF) and the 3′ noncoding region (Co-STND-U275, 5′-CCCGACGAGTTCGTGGTGGTG; Co-STND-L1529, 5′-GCGTTACACATTAGGGCTCTTC CATA). The product was cloned into vector pGEM-Teasy (Invitrogen, Carlsbad, CA), and serial dilutions of linearized plasmid were used to optimize the assay. RNA standards were generated by in vitro transcription of linearized plasmid DNA using a mMESSAGE mMACHINE T7 kit as recommended by the manufacturer (Ambion, Austin, TX). A portion of the construct (nucleotides 682–1105 of the N ORF) was modified through site-

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directed mutagenesis, to distinguish plasmid-derived products from authentic products in diagnostic applications. Mutations introduced were an A to G change at position 845 of the N ORF, and an A to C change at position 866, creating a unique *Apa*I restriction site.

Detection of live virus was assessed by using supernatant from virus-infected Vero E6 cells (isolate BJ01; 4th passage; 10^8 $TCID_{50}$/mL) tenfold diluted to 10^{-12} in tissue culture media. RNA from 140-µL aliquots of each dilution was extracted and resuspended in 60 µL of DEPC-treated water for reverse transcription (9 µL RNA/20-µL reaction) and PCR (5 µL/assay). 20 µL of each virus dilution were spiked into 180 µL of clarified supernatant of a fecal preparation to simulate clinical specimens, and RNA from 140-µL aliquots was extracted and processed as above.

Clinical materials, including 326 fecal and 426 whole blood samples, were collected from Chaoyang Hospital, 301 Hospital, You'an Hospital, and Xuanwu Hospital, Beijing. All persons had a diagnosis of probable SARS according to World Health Organization (WHO) criteria. For analysis of fecal samples, 1 g of stool was suspended in 1 mL of phosphate-buffered saline, mixed vigorously, and centrifuged for 10 min at 3,000 *g*, 4°C. Supernatant was collected for RNA extraction and PCR analysis. For analysis of blood samples, whole blood was fractionated using Ficoll Paque (Amersham Pharmacia, England). Plasma was collected and immunoglobulin (Ig) G and IgM levels were determined with an ELISA kit from the Beijing Genomics Institute (Beijing, China). Peripheral blood mononuclear cells were collected and RNA extracted by using the QiaAmp Viral RNA Mini Kit (Qiagen, Germany). Nine microliters total RNA was reverse transcribed (SuperScript II Transcriptase, Invitrogen), and 2 µL of cDNA subjected to PCR by using a TaqMan Universal Master Mix kit (PE Applied Biosystems) on an ABI Prism 7900 HT sequence detector (PE Applied Biosystems). Thermocycling conditions were: 2 min 50°C (AmpErase UNG), 10 min 95°C (polymerase activation); 45 cycles of 15s 95°C denaturation, and 1 min 60°C annealing/extension.

Conclusions

A standard curve of plasmid concentration versus threshold cycle was generated with a cloned version of the 3′ terminal portion of the viral genome. A correlation coefficient (r2) of 0.9913 showed a linear relationship between threshold cycle (Ct) and plasmid concentration (0–10^5 copies) (Figure 1A). The detection limit for plasmid DNA was ≤5 copies per assay (Ct = 42.66). A linear relationship was consistently obtained for input loads of 10^1–10^5 copies per assay.

Standards for RT-PCR were generated by in vitro transcription of RNA from linearized plasmid template with

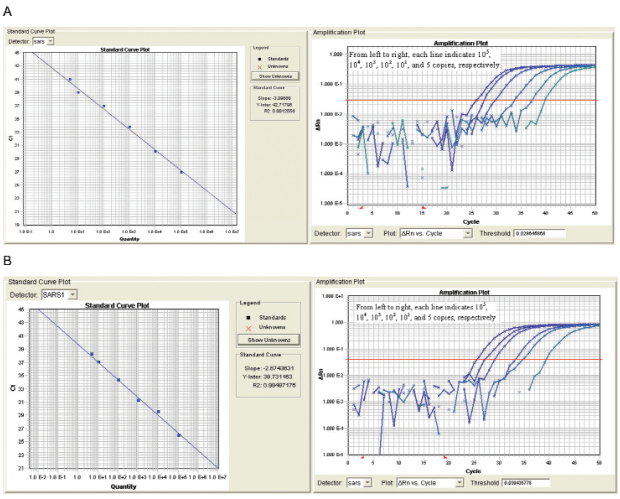

Figure 1. Standard curve and amplification plot using serial dilutions of plasmid DNA (A) or of cRNA (B).

T7 polymerase. Logarithmic dilutions of the synthesized RNA yielded results comparable to the DNA standards (r2 = 0.9950; Figure 1B).

Supernatant from infected Vero E6 cells was serially diluted to determine the detection limit for live virus. Analysis of RNA extracted from logarithmic dilutions indicated a detection threshold of 0.0005 $TCID_{50}$ (10^{-9} dilution; 0.1 $TCID_{50}$/mL; 0.0005 $TCID_{50}$ per assay well). The threshold for detection of SARS-CoV in spiked fecal samples was 0.005 $TCID_{50}$ (10^{-7} dilution; 1 $TCID_{50}$/mL; 0.005 $TCID_{50}$ per assay well) (data not shown).

Materials from persons who had probable SARS included 326 fecal samples and 426 blood samples. Control specimens collected during the outbreak from healthy persons included 16 fecal samples and 82 blood samples. The detection rate in fecal samples was 27% during the first 20 days after onset of symptoms (Table, Figure 2A). In the 20 days that followed, the detection rate declined to 16% to 18%, but even after >40 days, 9% of samples gave a positive reading. A similar time course was observed in the analysis of blood samples; however, a higher detection rate of 45% to 49% was obtained (note that only 11 of the samples were matched for blood and feces). During the first 20 days after onset of symptoms, the detection rate of RT-PCR in blood was significantly higher than that for IgM (10%–24%) or IgG antibodies (13%–15%) (Table, Figure 2B). Twenty-one to 40 days after onset of symptoms, serologic findings were more frequently positive than RT-PCR.

Of the 16 fecal and 82 blood samples obtained from healthy persons, one blood sample yielded a positive result in RT-PCR (confirmed by repeated assays). Because the sample was collected during the outbreak, it may represent a true infection in a person who was not yet symptomatic

Table. Summary of clinical samples

Specimens	Total patients	1–10 d		11–20 d		21–30 d		31–40 d		≥40 d	
		pos	neg	pos	neg	pos	neg	pos	neg	pos	neg
Feces PCR	326	10	27	19	52	12	65	12	55	7	67
Blood PCR	426	28	34	20	21	22	143	26	132	NA	NA
Blood IgG	426	6	56	10	31	82	83	138	20	NA	NA
Blood IgM	426	8	54	6	35	63	102	82	76	NA	NA

[a]pos, positive; neg, negative; PCR, polymerase chain reaction; Ig, immunoglobulin; NA, not available.

or who did not have classical symptoms (no clinical information for the period after sampling was available).

We also analyzed 180 sputum and 76 throat-washing samples from an unrelated cohort of persons with a diagnosis of probable SARS, for which the time after onset of symptoms had not been reported. The RT-PCR detection rate obtained in these samples was 63% for sputum samples, and 15% for throat washing samples (data not shown).

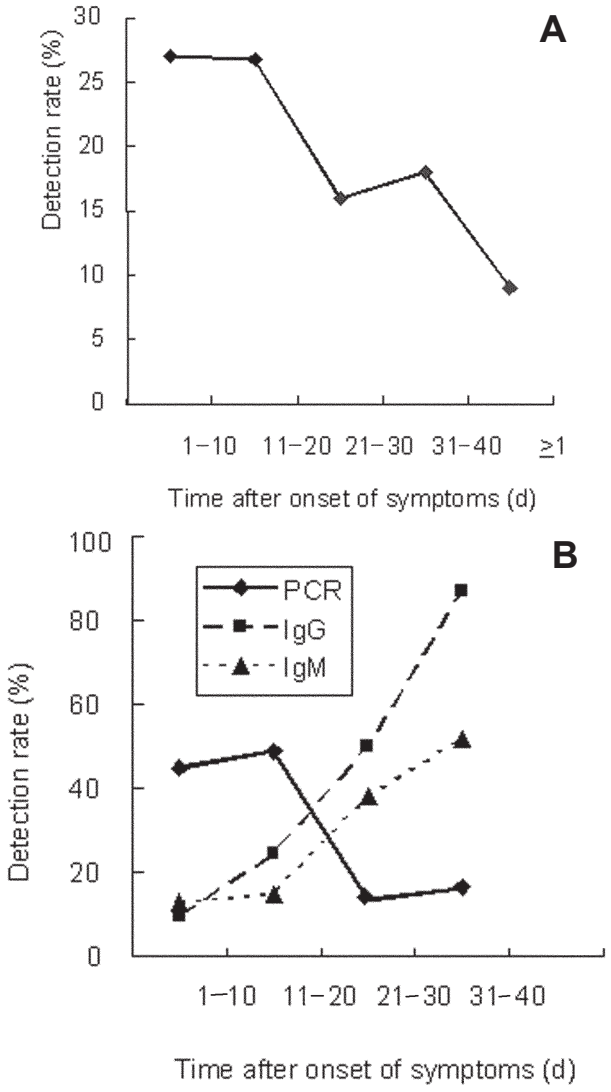

Figure 2. (A) real-time polymerase chain reaction (PCR) analysis of fecal samples; (B) real-time PCR, immunoglobulin (Ig) M and IgG analysis of blood samples.

It was not possible during the Beijing outbreak to obtain clinical materials in a prospective serial fashion from a defined SARS-CoV–infected patient cohort. Thus, some samples represent persons with respiratory symptoms caused by pathogens other than SARS-CoV (10). However, confidence in the clinical criteria is enhanced by an 87% seropositivity in samples taken 31–40 days after onset of symptoms.

Current real-time RT-PCR assays allow sensitive detection of SARS-CoV nucleic acid in clinical specimens by targeting N gene sequence, as shown here, or *pol* gene sequence (11–15). A major advantage to real-time PCR platforms is that amplification and analysis are completed in a closed system. Thus, the risk of contamination, which can confound conventional (frequently nested) RT-PCR protocols (5,11,16), is markedly reduced. Whether different positivity rates reported for various SARS-CoV assays (12–14,17) reflect true differences in assay performance, or merely differences in specimen type or differences in sample preparation (13), will only become apparent after comparative quality control tests using identical samples in the various assays and laboratories. Using calibrated DNA and RNA standards, we achieved comparable results with the assay reported here in the New York and Beijing laboratories.

RNA integrity is a critical determinant of sensitivity in RT-PCR SARS-CoV assays. Samples were not collected at clinical sites with the objective of nucleic acid analysis. Additionally, protocols adopted by the various hospitals for sample collection, handling, and storage were not uniform. Nonetheless, RT-PCR analysis resulted in consistent results for all 11 cases of matching feces and blood samples. Furthermore, all blood samples seropositive during the first 20 days after onset of symptoms were also positive in RT-PCR. Of the 48 RT-PCR positive samples collected 21–40 days after onset of symptoms, 45 were also seropositive.

RT-PCR analysis of blood was a less sensitive index of infection than immunologic assays at later time points (21–40 days after onset of symptoms). However, 16% of blood samples and 18% of fecal samples contained SARS-CoV RNA >31–40 days after onset of symptoms. A similar duration of persistence of SARS sequences in stool has been observed by Ren et al. (17). Whether infectious virus is present at these later time points remains to

be determined; nonetheless, our findings indicate that long-term monitoring may be required to control dissemination of disease.

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Serologic and Molecular Biologic Methods for SARS-associated Coronavirus Infection, Taiwan

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Severe acute respiratory syndrome (SARS) has raised a global alert since March 2003. After its causative agent, SARS-associated coronavirus (SARS-CoV), was confirmed, laboratory methods, including virus isolation, reverse transcriptase–polymerase chain reaction (RT-PCR), and serologic methods, have been quickly developed. In this study, we evaluated four serologic tests (neutralization test, enzyme-linked immunosorbent assay [ELISA], immunofluorescent assay [IFA], and immunochromatographic test [ICT]) for detecting antibodies to SARS-CoV in sera of 537 probable SARS case-patients with correlation to the RT-PCR . With the neutralization test as a reference method, the sensitivity, specificity, positive predictive value, and negative predictive value were 98.2%, 98.7%, 98.7%, and 98.4% for ELISA; 99.1%, 87.8%, 88.1% and 99.1% for IFA; 33.6%, 98.2%, 95.7%, and 56.1% for ICT, respectively. We also compared the recombinant-based western blot with the whole virus–based IFA and ELISA; the data showed a high correlation between these methods, with an overall agreement of >90%. Our results provide a systematic analysis of serologic and molecular methods for evaluating SARS-CoV infection.

Severe acute respiratory syndrome (SARS) is a new infectious disease with clinical symptoms indistinguishable from atypical pneumonia at the early stage of illness (1). Because of its relatively high transmissibility and mortality rate on infection, >8,400 SARS patients, including 810 deaths, have been reported by China, Vietnam, Hong Kong, Singapore, Canada, Taiwan, and other areas worldwide from March to July 2003 (2). As of July 31, 668 probable SARS case-patients, including 71 deaths, were reported to the Center for Disease Control, Taiwan (Center for Disease Control–Taiwan) (3). With the close cooperation of laboratories worldwide, the causative agent of SARS was quickly identified as a new coronavirus species, now referred to as SARS-associated coronavirus (SARS-CoV) (4–6). With epidemiologic evidence, droplet and close contact transmission are the major routes for the spread of SARS (7). Suspected SARS patients need to be quarantined and treated with intense care to minimize transmission to others. Therefore, sensitive and specific laboratory tests to differentiate SARS from other mild atypical pneumonia must be developed to shorten the quarantine period for contacts with SARS patients and further to contain SARS outbreaks.

Even though the RT-PCR is the most sensitive technique to detect early SARS-CoV infection, the positive predictive rate for probable SARS cases is only 37.5% according to our data (Center for Disease Control–Taiwan). The other reported probable SARS cases, therefore, still have to rely on serologic diagnosis. We analyzed the results from immunofluorescence assay (IFA), enzyme-linked immunosorbent assay (ELISA), neutralization test, and immunochromatographic test (ICT) to detect antibodies against SARS-CoV in serum specimens of patients with probable SARS in Taiwan. The results of neutralization tests, ELISA, and IFA were highly correlated.

Materials and Methods

Specimens

According to World Health Organization (WHO) criteria, a person seeking treatment after November 1, 2002, with a history of high fever (>38°C), coughing, or breathing difficulty, and having resided in or traveled to an area with recent local transmission of SARS during the 10 days before onset of symptoms was classified as a suspected case-patient. A suspected case-patient with radiographic evidence of infiltrates consistent with pneumonia or respiratory distress syndrome on a chest x-ray was considered a

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probable case-patient (8). In the study, 3,367 throat swab specimens from possible SARS patients reported to Center for Disease Control-Taiwan were tested for SARS-CoV by RT-PCR. Seven hundred and ninety-nine serum samples from 537 probable case-patients, fulfilling WHO criteria for probable SARS cases, were tested for antibodies to SARS-CoV by neutralization test, IFA, ELISA, and ICT. Of these patients, 262 had paired serum specimens, in which the acute- and convalescent-phase serum specimens were collected at day 1 to day 12 and at day 28 or more after the onset of illness, respectively. In the other 275 patients, only a single serum specimen was collected during their illness: 210 had the serum collected at the acute phase or at the early convalescent phase from day 1 to day 20, and 65 were collected during the late convalescent phase from day 28 to day 78 after the illness onset.

RT-PCR

The primers and probes used for SARS-CoV detection by RT-PCR and real-time RT-PCR were synthesized, according to the recommendations of the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, USA (5,9). The viral RNA from the throat swab specimens was extracted by the MagNA LC Pure and MagNA Pure LC total nucleic acid isolation kit (Rouche, Mannheim, Germany). After extraction, 5 μL of RNA extract was used as the template in all PCR assays in 50-μL reaction volumes containing 10 μL of 5X buffer, 2 μL enzyme mix, 2 μL deoxynucleoside triphosphate (dNTP), and 0.6 μM each of sense and antisense primer. The reaction was subjected to precycle condition at 50°C for 30 min, and 95°C for 15 min. Forty cycles of amplification were then conducted at 95°C for 30 s, 50°C for 40 s, and 72°C for 1 min. For real-time quantitative RT-PCR assays, a 20-μL reaction volumes containing 12 μL of HPA (human pneumonia–associated coronavirus)-Coronavirus LC Master mix, 3 μL of HPA-Coronavirus LC Mg-Sol, and 0.5 μL of HPA-Coronavirus LC internal control were thermal-cycled by a Light Cycler (Rouche) at 50°C, for 10 min for RT reaction, at 95°C for 10 min for denaturation, and followed by 45 cycles of amplification at 95°C for 2 s, 55°C for 12 s, and 72°C for 10 s.

Neutralization Test

Serum specimens were tested for neutralizing activity, according to the procedures described by Marx et al. (10), with modifications. The neutralization titer was determined in Vero E6 cells. Briefly, the serum specimens from patients with probable SARS were first incubated at 56°C for 30 min. Then, 50 μL of serial twofold diluted serum specimen, from 8-fold to 1,024-fold were added into equal volume of culture medium containing SARS-CoV (50 tissue culture infective dose [$TCID_{50}$] on a 96-well microtiter plate) and incubated at 37°C for 1 h. Finally, 100 μL of Vero E6 cells (2.5 x 10^5/μL) were added to each well of the plate. Cultures were held at 37°C and 5% CO_2 with daily observations for cytopathic effect (CPE). On day 5, the titer of antibody was calculated as the highest dilution that CPE was completely inhibited on the well. The neutralization test was carried out with each sample in duplicate along with both positive and negative controls. The positive control serum specimens were taken from patients with confirmed SARS in Taiwan, and the negative control serum specimens were from healthy volunteers. If a sample showed a 4-fold difference or greater in titers in the duplicated sample runs, it was judged as an invalid outcome and had to be retested. A sample is considered to be positive if its titer is ≥1:16 in the case of single serum group, and at least a 4-fold increase in titers between the acute- and convalescent-phase serum specimens in the paired specimens group.

IFA

IFA testing was performed by using a diluted serum specimen reacted against SARS-CoV-infected Vero E6 cells and uninfected Vero E6 cells. Vero E6 cells were grown in minimum essential medium (MEM) containing 10% fetal bovine serum at 37°C. At a density of 80%, the cells were infected with SARS-CoV ($TCID_{50}$, 10^6/mL). After CPE appeared, the cells were washed with 0.025% trypsin and spotted on slides for IFA as previously described (11). These slides were put in a closed heating container until completely drying, then were fixed in acetone for 15 min. 10 μL of 2-fold serial diluted serum starting from 1:100 to 1:800 was placed onto each well of the slide, and incubated at 37°C for 30 min. After being washed twice with phosphate-buffered saline (PBS), for 5 min each, 10 μL of 1:100 diluted specific antihuman gamma globulins labeled with FITC (Zymed) was added onto each well, and incubated at 37°C for 30 min. After washing twice with PBS, slides were observed under a fluorescence microscope. Criteria for a positive IFA result included reactivity to infected cells. A sample with an antibody titer of 1:100 is positive. Sera that did not react to infected cells were considered negative. If nonspecific reactivity to both infected and uninfected cells were detected, the test was considered un-interpretable.

ELISA

An ELISA for the detection of coronavirus has been described (12). In our study, the materials for the ELISA to detect SARS-CoV antibodies were provided by CDC in Atlanta. In brief, SARS-CoV Vero E6 cell lysates used as antigens were added to the top half of the wells in the plate overnight at 4°C. The Vero E6 cell lysates without SARS-CoV used as control antigens were simultaneously added

to the wells in the bottom half of the plate. On the following day, 100 μL of diluted serum (starting from 1:100 to 1:1,600) was added to both test and control wells. Then each well of the plate was incubated at 37°C for 60 min. After washing the plate 3 times with 250 μL of wash buffer in each well, add 100 μL of conjugate dilution (1:4,000 of goat anti-human immunoglobulin (Ig) A, IgG, and IgM) to each well and incubate the plate at 37°C for 60 min. Again after washing, 100 μL of the substrate (a 1:1 mixture of 2,2-azino-di [3-ethylbenzthiazoline] sulfonic acid [ABTS] and hydrogen peroxide) were added to each wells, and incubated at 37°C for 30 min. Place the plate on ELISA reader, and read at 410 nm. A sample is positive if its adjusted optical density (OD) value (OD of test – OD of control) exceeds the mean plus 3 standard deviations of the normal controls and its titer is ≥1:400.

ICT

The ICT generally refers to a rapid chromatographic technique based on a sandwich format using double antigens or double antibodies (13). The SARS-CoV rapid test we adopted is a newly developed immunogold-based ICT device (Tyson Bioresearch, Inc., Taipei, Taiwan). The antigen used in this test is a recombinant nucleocapsid (N) protein of SARS-CoV. The inside of the ICT device contains a nitrocellulose strip, on top of which is a detection zone. In the detection zone, the goat anti-mouse IgG and SARS-CoV N protein have been immobilized separately onto a control line and a test line. In the middle of the strip, the mouse IgG and SARS-CoV N protein are to be coupled respectively with some colloidal gold particles, which serve as a detector. At the bottom are two wells for the sample and the buffer, respectively. The ICT is carried out following the manufacture's instruction. Briefly, 15 μL of undiluted serum sample is added to the sample well, and 220 μL of testing buffer to the buffer well. When the sample contains specific antibodies to SARS-CoV, they will react first with the antigen-gold complex. After lateral flow along the membrane, a colored complex of antibodies-antigen-gold will deposit on the test line containing the fixed antigen. The red signal from the gold will gradually appear on the test line and become visible by naked eye. A positive result will show two parallel lines; the upper one is the control line, which shows that the device works fine and the lower one is the test line, which indicates that the serum sample contains SARS-CoV antibodies. In case of a negative result, only red will be seen on the control line. If red is found only at the test line or no lines are visible, the test is invalid.

Western Blot

The preparation of recombinant proteins of SARS-CoV and the procedures for Western blot assay have been described recently (14). Briefly, the amplified gene products of SARS-CoV including N, M (membrane), and S (spike), were gel purified and cloned into the pQE30 expression vector (Qiagen, Valancia, CA). The constructs were then transformed into *Escherichia coli* JM109 cells (Invitrogen, Carlsbad, CA). After induction by isopropyl-β-D-thiogalactopyranoside, the cells were sonicated, and the recombinant proteins were extracted with 1.5% sarcosine. Finally these recombinant proteins were bound by BD TALON metal affinity resins (BD Biosciences, San Jose, CA) and examined by 12% sodium dodecyl sulfate–polyacrylamide gel electrophoresis. The Western blot assay was carried out to examine the pattern of antibody development against different recombinant proteins of SARS-CoV.

Results

Detection of Viral RNA of SARS-CoV by RT-PCR

A total of 3,367 possible SARS patients were reported to Center for Disease Control-Taiwan from March 10 through the end of July 2003. Of which, 668 were probable case-patients, 1,331 were suspected case-patients, 1,036 were rejected, and 332 case-patients were removed from reporting (Table 1). Throat swabs were collected from 590 of the 668 patients with probable cases. Of them, 221 had positive results on PCR, giving a positive rate of 37.5%. Throat swabs were also collected from 1,043 of the 1,331 patients with suspected cases. Of them, 38 had positive results by PCR, giving a positive rate of 3.6%. Figure 1 shows the PCR-positive rates of the throat swab specimens taken from patients with probable SARS between day 1 and day 13 after the illness onset. On the first day of onset, RT-PCR detected positive results in 32% of patients with suspected cases. The positive rates reached a peak of 50% to 60% on day 7 to day 10 and declined thereafter. However in a few specimens, virus RNA was still detected on day 18, day 20, and day 38 after illness onset (data not shown).

Detection of Antibodies to SARS-CoV in Probable SARS Patients

Figure 2 shows when antibodies to SARS-CoV appeared during the infection. Although in samples from 10% (14/138) of the probable case-patients, antibodies to SARS-CoV could be detected during the acute phase of illness (day 1 to day 7) by neutralization test, IFA, or ELISA, antibodies against SARS-CoV developed in most at the late convalescent stage. The positive rate of antibodies to SARS-CoV was raised to 50% at 3 weeks after illness onset and reached to a peak of over 70% at 10 weeks after onset. The overall antibody-positive rate was 54.2% (254/469).

Table 1. Positive rates of RT-PCR for SARS-CoV in reported SARS cases in Taiwan

Classification of reported cases	Case no.	Specimens collected[a]	No. PCR (+)	Positive rate (%)
Probable	668	590	221	37.5
Suspected	1,331	1,043	38	3.6
Ruled out	1,036	907	7	0.8
Reporting cancelled	332	229	1	0.4
Total	3,367	2,769	267	9.6

[a]Throat swab specimens were used for RT-PCR (reverse transcriptase–polymerase chain reaction). SARS-CoV, severe acute respiratory syndrome–associated coronavirus.

Relative Values of Different Serodiagnostic Methods

Of the total 537 probable SARS case-patients, 469 had been tested for the antibody response to SARS-CoV by neutralization test, ELISA, and IFA in parallel, but only 244 patients were tested by ICT. With neutralization tests as a reference method, the overall characteristics of the evaluated methods, including ELISA, IFA, and ICT, are given in Table 2. For ELISA, the sensitivity was measured at 98.2%. Of the 224 serum specimens, which tested positive with neutralization test, 4 gave negative responses with ELISA. The specificity, positive predictive value, and negative predictive value were 98.7%, 98.7%, and 98.4%, respectively. For IFA, the sensitivity was evaluated at 99.1%. Two serum samples, which had been positive in neutralization test, were negative with IFA. The specificity, positive predictive value, and negative predictive value were of 87.8%, 88.1%, and 99.1%, respectively. The specificity of the ICT was calculated to be 98.2%; however, its sensitivity (33.6%) was low, leading to a negative predictive value of 56.1%. In the total of 245 negative neutralization tests, 3 positive results were detected with ELISA, 30 positive with IFA, and 2 positive with ICT tests. These 35 specimens were taken from 31 patients, in which two positive PCR results were found.

Cross-Reactions with the Non-SARS Panel

Ten normal serum samples from healthy volunteers tested negative for antibodies against SARS-CoV by neutralization test, IFA, ELISA, and ICT. In addition, 24 serum samples from patients with other diseases were used as a specificity panel to analyze whether these assays showed any cross reactions with SARS-CoV. These patients were definitely confirmed as non-SARS-CoV–associated diseases. As shown in Table 3, no positive results were detected to these serum specimens, and the measurements of specificity were all 100% for the neutralization test, ELISA, IFA, and ICT.

Values of RT-PCR and Neutralization Test

Table 4 compares results of the RT-PCR and the neutralization test in specimens from probable SARS case-patients. In this comparison, throat swab specimens from 381 probable SARS case-patients were used for RT-PCR, and their convalescent-phase serum specimens, collected on day 28 or longer after illness onset, were tested with neutralization test. Of the 207 cases, which were positive by neutralization test, 145 were tested positive with RT-PCR. The sensitivity, specificity, positive predictive value, and negative predictive value of RT-PCR compared with results with neutralization test were of 52.2%, 78.7%, 74.5%, and 58.1%, respectively.

Laboratory Confirmation Rate for Probable SARS Case-Patients

Table 5 shows the laboratory confirmation rate of probable SARS cases in Taiwan. With 469 probable case-

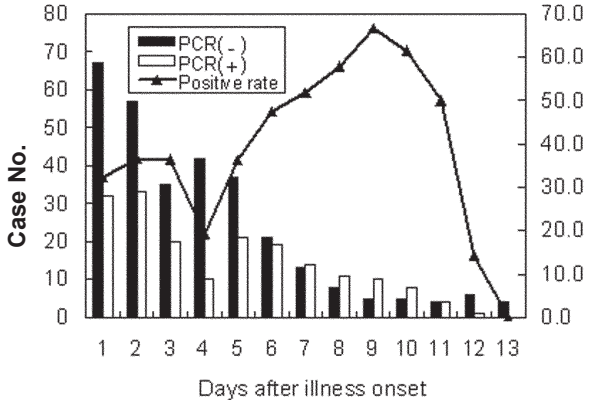

Figure 1. Polymerase chain reaction–positive rates of throat swab specimens collected on different days from probable SARS cases. If a patient had two or more specimens, the patient was only counted once.

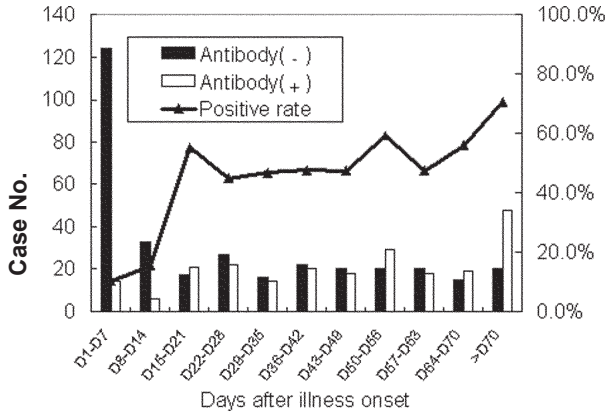

Figure 2. Antibody-positive rate of serum specimens collected on different days from probable SARS case-patients. If a patient had two or more specimens, the patient was only counted once.

Table 2. Specificity, sensitivity, positive and negative predictive values of the tests evaluated for the serodiagnosis of SARS, in comparison to the neutralization test[a,b]

			Neutralization test		Performances of methods evaluated			
Method	Results	No.	Positive	Negative	Sensitivity	PPV	Specificity	NPV
ELISA	Positive	223	220	3	98.2%	98.7%	98.7%	98.4%
	Negative	246	4	242				
IFA	Positive	252	222	30	99.1%	88.1%	87.8%	99.1%
	Negative	217	2	215				
ICT[c]	Positive	46	44	2	33.6%	95.7%	98.2%	56.1%
	Negative	198	87	111				

[a]N = 469.
[b]SARS, severe acute respiratory syndrome; PPV, positive predictive value; NPV, negative predictive value; ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescent assay; ICT, immunochromatographic test.
[c]Only 244 serum samples were used for immunochromatographic test assay.

patients tested, the positive rate of RT-PCR is 33.7% (158/469). These patients had been also tested for the antibody response to SARS-CoV by neutralization test, ELISA, and IFA, but only 244 were tested by ICT. The seropositive rate for ELISA, IFA, neutralization test, and ICT were 47.5% (223/469), 57.7% (252/469), 47.8% (224/469), and 16.8% (41/224), respectively. If these results were combined with existing RT-PCR results, the laboratory confirmation rates of probable SARS cases went up to 57.4% (269/469), 63.3% (297/469), 57.8% (271/469), and 42.4% (103/244), respectively.

Recombinant Antigens for SARS Serologic Diagnosis

As discussed above, all the neutralization tests, ELISA, and IFA are based on the whole viral extracts of SARS-CoV. Therefore, antigens for these serologic tests must be prepared in the biosafety level 3 laboratory. To provide a convenient tool and decrease the risk of infection, a Western blot with several SARS-CoV recombinant proteins was developed and evaluated. Cloned peptides carrying epitopes can be produced on a large scale and with an acceptable degree of purity. Table 6 shows the comparison of recombinant protein-based Western blot with whole virus-based IFA, and ELISA. Ninety-five serum samples were used in this comparison. The sensitivities, specificities and overall agreements of Western blot were 91.3%, 89.88%, and 90.5%, compared with IFA results; 97.6%, 88.8%, and 92.6%, compared with ELISA results.

Discussion

The study shows that in the first 2-week period after onset of SARS, RT-PCR is the most sensitive method of detecting the virus RNA, and the positive rate is the highest. However, during the convalescent phase of the disease, detecting antibodies in serum specimens is more important than detecting viral RNA. Four serologic diagnostic methods, including neutralization test, ELISA, IFA, and ICT were each evaluated and compared for antibody responses to SARS-CoV infection, in which the neutralization test was held as a reference method. The specificity of these methods is extremely good (100%), since no cross-reactions were detected with a non-SARS disease panel.

However, some variations in sensitivity, positive predictive value, and negative predictive value were found among these methods. As shown in Table 2, ELISA results were highly correlated with results from the reference method, the neutralization test. The measured performance of ELISA was so outstanding, with the sensitivity, specificity, positive predictive value, and negative predictive value levels exceeding 98%, that ELISA was chosen as a

Table 3. Specificity of the tests evaluated for the serodiagnosis of SARS, in comparison to the neutralization test with regards to samples which tested positive for other diseases[a,b]

Pathogen	Parameter	Number	Positive	Negative	Positive	Specificity	Positive	Specificity	Positive	Specificity
Hepatitis B virus	HBs IgM	3	0	3	0	100%	0	100%	0	100%
Hepatitis C virus	IgM	3	0	3	0	100%	0	100%	0	100%
Adenovirus	Total Ab	1	0	1	0	100%	0	100%	0	100%
Influenza A virus	Total Ab	3	0	3	0	100%	0	100%	0	100%
Influenza B virus	Total Ab	1	0	1	0	100%	0	100%	0	100%
Dengue virus	IgM	2	0	2	0	100%	0	100%	0	100%
JEV	IgM	1	0	1	0	100%	0	100%	0	100%
Hantavirus	Total Ab	1	0	1	0	100%	0	100%	0	100%
Chlamydia pneumoniae	IgM	4	0	4	0	100%	0	100%	0	100%
Mycoplasma pneumoniae	IgM	4	0	4	0	100%	0	100%	0	100%
Streptococcus pneumoniae	Total Ab	1	0	1	0	100%	0	100%	0	100%
Total non-SARS pathogens		24	0	24	0	100%	0	100%	0	100%

[a]SARS, severe acute respiratory syndrome; ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescent assay; JEV, Japanese encephalitis virus; HB, hepatitis B; AB, antibody; Ig, immunoglobulin.
[b]N = 469

Table 4. Specificity, sensitivity, positive and negative predictive values of the RT-PCR for the diagnosis of SARS, in comparison to the neutralization test with convalescent-phase serum specimens[a]

			Neutralization test		Performances of methods evaluated			
Method	Results	No.	Positive	Negative	Sensitivity	PPV[b]	Specificity	NPV[b]
RT-PCR	Positive	145	108	37	52.2%	74.5%		
	Negative	236	99	137			78.7%	58.1%

[a]SARS, severe acute respiratory symptoms; RT-PCR, reverse transcriptase–polymerase chain reaction; PPV, positive predictive value; NPV, negative predictive value.
[b]The serum specimens of 28 days and more after the illness onset in probable SARS case-patients were tested in this comparison.

confirmation alternative. In the case of IFA, both the sensitivity and negative predictive value levels were above 99%; however, the specificity of 87.8% implies that IFA may cause false-positive problems. Therefore, a weak positive IFA result should be retested by a neutralization test or ELISA. The ICT, though simple and quick to perform, is lacking in adequate sensitivity in our evaluation. Therefore, it was not a reliable test for detecting of antibodies to SARS-CoV.

Since the neutralization test, ELISA, and IFA all use whole virus particles as the antigen, for safety reasons the preparation of SARS-CoV antigen must be conducted in a biosafety level 3 laboratory, which will prevent these test methods from being widely applied. Therefore, the trend in method development may lead toward the manufacturing of antigens with certain recombinant proteins. In this study, we compared a recombinant-based Western blot with the whole virus-based IFA and ELISA, and the data showed a high degree of correlation between these methods, with an overall agreement above 90% (Table 6). Thus, using these recombinant antigens may become a much safer alternative to detect antibodies against SARS-CoV.

Eight PCR-positive specimens were found in the group of the ruled out and group of those that were reported canceled (Table 1), and they were selected to test for antibodies to SARS-CoV by using acute-phase serum samples between day 1 and day 4 after the illness onset. However, no positive result was found by any of the IFA, ELISA, and neutralization test. Since no convalescent-phase serum specimens were collected from those patients, we do not know the negative results are truly negative or just resulted from the timing of gathering specimens when no antibodies were produced. Moreover, another 95 samples from the ruled-out category had been tested with ELISA, but no positive results were found. In addition, 283 specimens from 1,036 case-patients with suspected SARS were also assayed with ELISA and the neutralization test. Of them, 45 were positive with a positive rate of 15.9% (45/283). Among the 35 PCR-positive specimens in the suspected SARS category, 10 were also positive in detection of antibodies to SARS-CoV.

Finally, in this study, the overall antibody positive rate for probable SARS patients was 54.2%. This rate was much lower than that reported in Hong Kong, which showed that the IgG seroconversion to SARS coronavirus was as high as 93% (70/75) at day 28 after the illness onset (15). This difference may come from some different circumstances between Hong Kong and Taiwan. In the SARS outbreak of Hong Kong, the index case-patient and the infectious source leading to the outbreak were quite clear, and 75 patients were admitted to the same hospital within 4 days. From the epidemiologic point of view, therefore, the SARS outbreak was a typical cluster outbreak. In Taiwan, the samples from probable SARS case-patients were collected from over 50 hospitals between March and June 2003. Some might not have been true SARS patients but were reported as probable SARS cases. This result is

Table 5. Laboratory confirmation rate in probable SARS cases, in combination of RT-PCR with different serologic methods[a]

Results	ELISA	IFA	Neutralization test	ICT
PCR (+)	33.7% (158/469)	33.7% (158/469)	33.7% (158/469)	35.7% (87/244)
Antibody (+)	47.5% (223/469)	57.7% (252/469)	47.8% (224/469)	16.8% (41/244)
PCR (+) or antibody (+)	57.4% (269/469)	63.3% (297/469)	57.8% (271/469)	42.4% (103/244)

[a]SARS, severe acute respiratory syndrome; ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescent assay; ICT, immunochromatographic test; PCR, polymerase chain reaction.

Table 6. Comparison of recombinant protein–based Western blot with whole virus–based IFA and ELISA[a]

			IFA					ELISA				
Method	Results	Number	Positive	Negative	Sensitivity	Specificity	Overall agreement[b]	Positive	Negative	Sensitivity	Specificity	Overall agreement[b]
Western blot	Positive	47	42	5	91.3%	89.8%	90.5%			97.6%	88.8%	92.6%
	Negative	48	4									

[a]IFA, immunofluorescent assay; ELISA, enzyme-linked immunosorbent assay.
[b]Sum of the number of true positives and true negatives divided by total serum samples.

likely due to the policy that suspicious SARS cases were to be reported to local health agency within 24 hours in Taiwan or the clinician who attended the patients would have been fined. In September 2003, according to the WHO criteria and the laboratory data, 346 patients were reclassified as probable SARS patients by the Center for Disease Control–Taiwan, and these data were readily accepted by WHO on September 26, 2003 (16). With this new classification, the positive rate of antibodies to SARS-CoV in probable SARS patients in Taiwan was increased to 86.6% (227/262), by using the serum samples on day 28 or beyond after the onset of illness. These rates are closer to, though still lower than, rates from Hong Kong. Samples from the remaining 322 cases, excluded from the category of probable SARS cases, may have to be tested for other pathogens, such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae,* and human metapneumovirus to clarify a diagnosis.

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Real-Time Reverse Transcription–Polymerase Chain Reaction Assay for SARS-associated Coronavirus

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A real-time reverse transcription–polymerase chain reaction (RT-PCR) assay was developed to rapidly detect the severe acute respiratory syndrome–associated coronavirus (SARS-CoV). The assay, based on multiple primer and probe sets located in different regions of the SARS-CoV genome, could discriminate SARS-CoV from other human and animal coronaviruses with a potential detection limit of <10 genomic copies per reaction. The real-time RT-PCR assay was more sensitive than a conventional RT-PCR assay or culture isolation and proved suitable to detect SARS-CoV in clinical specimens. Application of this assay will aid in diagnosing SARS-CoV infection.

In late 2002, a life-threatening febrile respiratory illness appeared in Guangdong Province, China, and quickly spread throughout Asia and to other parts of the world (1–4). Designated "severe acute respiratory syndrome" (SARS), the etiologic agent was later identified as a hitherto unrecognized coronavirus (SARS-CoV) (5,6). A diagnosis of SARS is based primarily on clinical and epidemiologic criteria, but many respiratory viruses can cause similar symptoms, and therefore rapid, reliable diagnostic tests for SARS-CoV infection were needed. In response to this need, three types of diagnostic tests for SARS-CoV were quickly developed: tissue culture isolation, antibody detection, and reverse transcription-polymerase chain reaction (RT-PCR) assays.

A variety of RT-PCR assays were developed during the epidemic for SARS-CoV (1,5–8), including a commercial ready-to-use RT-PCR kit (Artus Biotech, Hamburg, Germany). Early RT-PCR assays based on conventional designs required postamplification product processing (e.g., gel electrophoresis), were time-consuming, and were prone to false-positive results from amplicon contamination. Conversely, real-time RT-PCR assays based on detecting and quantifying a fluorescent signal generated during amplification do not require postamplification processing and therefore eliminate one potential avenue for template contamination.

A variant of the real-time format, based on TaqMan probe hydrolysis technology (Applied Biosystems, Foster City, CA), has been shown to provide sensitive, specific, and quantifiable results in viral diagnostic assays (9) and has been used successfully to study emerging virus infections (10,11), including SARS (6,12). In response to the SARS public health emergency, we developed and evaluated a TaqMan real-time RT-PCR assay based on three distinct targets in the SARS-CoV genome for rapid deployment to the National Laboratory Response Network for Bioterrorism (LRN) (http://www.cdc.gov/programs/bio.htm).

Materials and Methods

Clinical Specimens

A total of 340 clinical specimens collected from 246 persons with confirmed or suspected SARS-CoV infection (13) were used in this study. Specimens included oro- and nasopharyngeal swabs (dry and in viral transport media), sputa, nasal aspirates and washes, bronchoalveolar lavage, and lung tissue specimens collected at autopsy. Specimen processing was performed in a class II biological safety cabinet using biosafety level three (BSL3) work practices. Three 100-µL aliquots of each specimen were distributed to vials each containing 900 µL of NucliSens lysis buffer (bioMérieux, Durham, NC) and stored at –70°C until testing.

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Virus Culture

Vero E6 cells were inoculated with clinical specimens and observed for cytopathic effect, consisting of cell rounding with a refractive appearance followed by detachment from the flask surface (5). Plaque titrations were conducted by standard methods (14).

Nucleic Acid Extraction

Nucleic acids were recovered from clinical specimens using the automated NucliSens extraction system (bioMérieux). Following manufacturer's instructions, specimens received in NucliSens lysis buffer were incubated at 37°C for 30 min with intermittent mixing, and 50 µL of silica suspension, provided in the extraction kit, was added and mixed. The contents of the tube were then transferred to a nucleic acid extraction cartridge and processed on an extractor workstation. Approximately 40–50 µL of total nucleic acid eluate was recovered into nuclease-free vials and either tested immediately or stored at –70°C.

Primers and Probes

Multiple primer and probe sets were designed from the Urbani strain of SARS-CoV polymerase 1b and nucleocapsid gene sequences (15) by using Primer Express software version 1.5 or 2.0.0 (Applied Biosystems) with the following default settings: primer melting temperature (T_M) set at 60°C; probe T_M set at 10°C greater than the primers at approximately 70°C; and no guanidine residues permitted at the 5′ probe termini. All primers and probes were synthesized by standard phosphoramidite chemistry techniques at the Biotechnology Core Facility at the Centers for Disease Control and Prevention (CDC). TaqMan probes were labeled at the 5′-end with the reporter molecule 6-carboxy-fluorescein (FAM) and at the 3′-end with the quencher Blackhole Quencher 1 (Biosearch Technologies, Inc., Novato, CA). Optimal primer and probe concentrations were determined by cross-titration of serial twofold dilutions of each primer against a constant amount of purified SARS-CoV RNA. Primer and probe concentrations that gave the highest amplification efficiencies in this study were selected for further study (Table 1).

Real-Time RT-PCR Assay

The real-time RT-PCR assay was performed by using the Real-Time One-Step RT-PCR Master Mix (Applied Biosystems). Each 25-µL reaction mixture contained 12.5 µL of 2X Master Mix, 0.625 µL of the 40X MultiScribe and RNase Inhibitor mix, 0.25 µL of 10 µM probe, 0.25 µL each of 50 µM forward and reverse primers, 6.125 µL of nuclease-free water, and 5 µL of nucleic acid extract. Amplification was carried out in 96-well plates on an iCycler iQ Real-Time Detection System (Bio-Rad, Hercules, CA). Thermocycling conditions consisted of 30 min at 48°C for reverse transcription, 10 min at 95°C for activation of the AmpliTaq Gold DNA polymerase, and 45 cycles of 15 s at 95°C and 1 min at 60°C. Each run included one SARS-CoV genomic template control and at least two no-template controls for the extraction (to check for contamination during sample processing) and one no-template control for the PCR-amplification step. As a control for PCR inhibitors, and to monitor nucleic acid extraction efficiency, each sample was tested by real-time RT-PCR for the presence of the human ribonuclease (RNase) P gene (GenBank accesssion number NM_

Table 1. Primers and probes used for real-time RT-PCR assays[a]

Assay ID	Primer/ probe	Sequence (5′>3′)	Genomic region	Location[b]
Primary diagnostic assay				
SARS1	F	CAT GTG TGG CGG CTC ACT ATA T	RNA polymerase	15370-15392
	R	GAC ACT ATT AGC ATA AGC AGT TGT AGC A		15422-15449
	P	TTA AAC CAG GTG GAA CAT CAT CCG GTG		15395-15420
SARS2	F	GGA GCC TTG AAT ACA CCC AAA G	Nucleocapsid	28531-28552
	R	GCA CGG TGG CAG CAT TG		28581-28597
	P	CCA CAT TGG CAC CCG CAA TCC		28559-28574
SARS3	F	CAA ACA TTG GCC GCA AAT T	Nucleocapsid	29016-29034
	R	CAA TGC GTG ACA TTC CAA AGA		29063-29083
	P	CAC AAT TTG CTC CAA GTG CCT CTG CA		29036-29061
To confirm positive results				
N3	F	GAA GTA CCA TCT GGG GCT GAG	Nucleocapsid	28432-28452
	R	CCG AAG AGC TAC CCG ACG		28383-28400
	P	CTC TTT CAT TTT GCC GTC ACC ACC AC		28406-28431
3′NTR	F	AGC TCT CCC TAG CAT TAT TCA CTG	3′ nontranslated region	29619-29642
	R	CAC CAC ATT TTC ATC GAG GC		29576-29595
	P	TAC CCT CGA TCG TAC TCC GCG T		29597-29618
M	F	TGT AGG CAC TGA TTC AGG TTT TG	Membrane protein	26951-26973
	R	CGG CGT GGT CTG TAT TTA ATT TA		27005-27027
	P	CTG CAT ACA ACC GCT ACC GTA TTG GAA		26974-27000

[a]RT-PCR, reverse transcription–polymerase chain reaction; F, forward primer; R, reverse primer; P, probe.
[b]Location based on the severe acute respiratory syndrome–associated coronavirus, Urbani strain (GenBank accession no. AY278741).

006413) by using the following primers and probe: forward primer 5′-AGATTTGGACCTGCGAGCG-3′; reverse primer 5′-GAGCGGCTGTCTCCACAAGT-3′; probe 5′-TTCTGACCTGAAGGCTCTGCGCG-3′. The assay reaction was performed identically to that described above except that primer concentrations used were 30 µM each. Fluorescence measurements were taken and the threshold cycle (C_T) value for each sample was calculated by determining the point at which fluorescence exceeded a threshold limit set at the mean plus 10 standard deviations above the baseline. A test result was considered positive if two or more of the SARS genomic targets showed positive results ($C_T \leq 45$ cycles) and all positive and negative control reactions gave expected values.

Clinical specimens submitted to CDC for SARS-CoV testing that gave positive results were confirmed with a TaqMan real-time RT-PCR assay based on three different primer and probe sets (Table 1). This assay was performed independently in a separate laboratory using newly extracted nucleic acid from a second specimen aliquot. The confirmatory assay used the SuperScript One-Step RT-PCR (Invitrogen Corp., Carlsbad, CA) and the Mx4000 Multiplex Quantitative PCR system (Stratagene, La Jolla, CA).

Synthesis of RNA Transcripts

Template for the nucleocapsid gene RNA was plasmid DNA (pCRII, Invitrogen Corp.) containing a full-length copy of the open reading frame for the SARS-CoV nucleocapsid gene oriented behind a T7 promoter. The plasmid was linearized by digestion with *Spe*I. The template for the polymerase RNA was a RT-PCR product generated by using the following primers: Cor-p-F2-T7, 5′-GTAATA CGACTCACTATAGGGCTAACATGCTTAGGATAA TGG-3′ and Cor-p-R2, 5′-CCTATTTCTATAGAGACA CTC-3′. Approximately 1 µg of RNA from Vero cells infected with SARS-CoV was used in RT-PCR reactions performed by using the SuperScript RT-PCR kit (Invitrogen Corp.) according to the manufacturer's instructions; both templates were purified by phenol-chloroform extraction and ethanol precipitation before being used for in vitro transcription. RNA was synthesized in vitro by using the MegaScript kit (Ambion Inc., Austin, TX) according to the standard protocol. Synthetic RNA was treated with RNase-free DNase before being purified by phenol-chloroform extraction and ethanol precipitation. The concentration of RNA was determined by use of UV spectroscopy. Synthetic RNA was positive sense and 1,369 nt in length for N and 325 nt in length for polymerase.

Results

Real-Time RT-PCR Sensitivity and Reproducibility

Tenfold serial dilutions of the polymerase and nucleocapsid RNA transcripts were tested to assess the copy detection limits and dynamic range of our optimized real-time RT-PCR assays. The lower potential limit of detection was approximately 2 transcript copies per reaction for SARS2 and SARS3, and 7.5 copies per reaction for SARS1 (Figure). The confirmatory assays, which employ three different primer and probe sets (N3, 3′NTR, and M), showed potential limits of detection similar to the SARS2 and SARS3 assays. Strong linear correlations ($r^2 \geq 0.99$) were obtained between C_T values and transcript quantity over at least a 6-log range from approximately 10^2 to 10^7

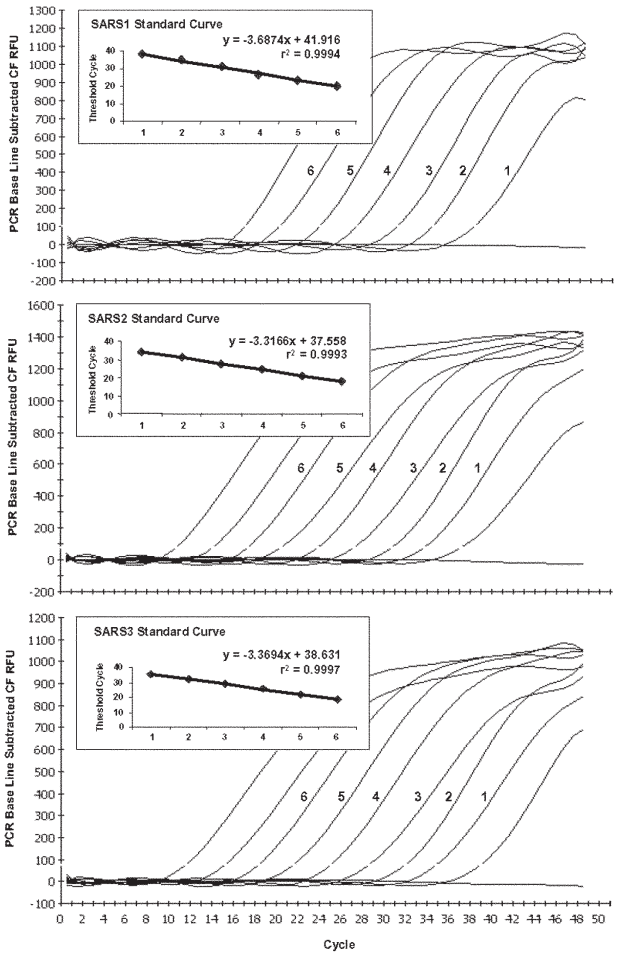

Figure. Typical amplification plot derived from serial 10-fold dilutions of severe acute respiratory syndrome–associated coronavirus RNA transcripts using TaqMan reverse transcription–polymerase chain reaction primer/probe sets SARS1, SARS2, and SARS3. A PCR Base Line Subtractive Curve Fit view of the data is shown with relative fluorescence units (RFU) plotted against cycle number. The default setting of 10 times the standard deviation of fluorescence in all wells over the baseline cycles was used to calculate the threshold cycle, or CT value, for a positive reaction (horizontal line). Inserts show standard curve analysis of the RNA amplification plots with CT values plotted against starting copy number. Plots derived from dilutions containing 2 x 10^6 to 20 transcript copies for SARS2 and SARS3, and 7.5 x 10^6 to 75 copies for SARS1.

copies per reaction for the three primer/probe sets. Linearity was markedly reduced for copy numbers exceeding 10^6 (data not shown).

Assay reproducibility was tested by using replicate 10-fold serial dilutions of the RNA transcripts and intra- and interassay variability evaluated for each dilution point in triplicate on three different days. At the lower copy detection limit for SARS2 and SARS3 (2 copies per reaction), assay reproducibility exceeded 90%. In contrast, the lower copy detection limit for SARS1 (7.5 copies per reaction) was positive in <50% of replicate reactions. One hundred percent reproducibility with SARS1 was achieved at the dilution that contained 75 transcript copies per reaction. Over the linear range of the assay, the coefficient of variation of the mean C_T values within and between runs was 0.46%–2.54% and 0.64%–2.39%, respectively (Table 2).

To assess the efficiency of amplification of the RNA transcripts in the presence of exogenous nucleic acid and potential RT-PCR inhibitors, 10-fold serial dilutions of the RNA transcripts were prepared in water and pooled total nucleic acid extract from 20 SARS-CoV–negative human respiratory specimens (nasopharyngeal aspirates, bronchial washes, sputum, naso- and oropharyngeal swabs, and lung tissue). Exogenous nucleic acid had no discernible effect on amplification efficiency of the SARS1 and SARS3 primer/probe sets, as demonstrated by the similarity in linear regression slopes and endpoint detection limits in the presence and absence of specimen extract (Table 3). In contrast, the standard curve for SARS2 had a more efficient slope (–3.21) in water than in the presence of spiked extract (–3.48) and with greater variation in the C_T values at 20 target copies or lower, suggesting that the amplification reaction was less efficient in the presence of the specimen extract. This observation was confirmed on two additional repetitions of the same experiment.

The real-time RT-PCR assay was compared with a previously described conventional RT-PCR for SARS-CoV by using fluorescent dye-labeled primers and GeneScan amplicon analysis (5). Tenfold serial dilutions of a pretitrated SARS-CoV stock adjusted to 1 x 10^7 PFUs/mL were prepared in triplicate and tested by all assays (Table 4). The real-time RT-PCR assays were positive with 100% frequency at a 10^{-8} dilution. Accordingly, the lowest virus quantity detected was 0.01 PFU/100 µL of specimen extract. The conventional RT-PCR assay was at least 10-fold less sensitive in repeat comparisons.

Specificity

We compared our primer and probe sets with sequences for 14 SARS-CoV field isolates that became available during the course of this study (16) and found no nucleotide mismatches. In contrast, alignments with other published human and animal coronaviruses (GenBank accession no.: human coronaviruses X69721 and AF124989; bovine coronaviruses NC003045 and AF124985; murine hepatitis viruses NC001846 and M55148; sialodacryoadenitis virus AF124990; canine coronavirus AF124986; feline infectious peritonitis virus AF124987; porcine hemagglutinating encephalomyelitis virus AF124988, Z34093, and AF124992; turkey coronavirus AF124991; and avian infectious bronchitis virus NC_001451) showed little sequence identity with our primer and probe sets. To further assess the potential for crossreactions with other members of the *Coronaviridae* family, the RT-PCR assays were tested against nucleic acid extracts of human respiratory coronaviruses OC43 (VR-759) and 229E (VR-740), feline infectious peritonitis virus (VR-3004), mouse hepatitis virus (VR-1426), bovine coronavirus (VR-874), porcine transmissible gastroenteritis virus (VR-743), and avian infectious bronchitis virus (VR-841), obtained from the American Type Culture Collection (Manassas, VA), and human enteric coronavirus (VR-1475). In addition, nucleic acid extracts of field isolates of influenza A and B; parainfluenza 1, 2, and 3; rhinovirus; adenovirus; human metapnuemovirus; and respiratory syncytial virus, as well

Table 2. Reproducibility of real-time RT-PCR assays[a]

	RNA transcript copy number[b]					
	7.5 x 10^1	7.5 x 10^2	7.5 x 10^3	7.5 x 10^4	7.5 x 10^5	7.5 x 10^6
SARS1						
CV within assay (%)[c]	2.53	0.96	0.49	0.69	1.66	0.7
CV between assays (%)[d]	2.39	1.09	0.82	0.64	2.1	0.79
	2.0 x 10^1	2 x 10^2	2 x 10^3	2 x 10^4	2 x 10^5	2 x 10^6
SARS2						
CV within assay (%)	1.27	0.57	0.46	0.72	0.84	0.67
CV between assays (%)	1.54	1.18	0.93	1.47	1.54	1.32
SARS3						
CV within assay (%)	0.8	0.55	0.65	0.5	0.27	1.25
CV between assays (%)	0.94	0.64	1.07	1.13	1.24	1.65

[a]RT-PCR, reverse transcription–polymerase chain reaction; CV, coefficient of variation.
[b]Ten-fold dilutions of the polymerase and nucleocapsid RNA transcripts; copies per reaction; dilution series thawed on 3 different days and assays performed in triplicate for each dilution.
[c]Determined from three replicates within each assay.
[d]Determined from three independent assays performed on different days.

Table 3. Efficiency of real-time PCR assays

	Mean C_T[b] values at estimated RNA transcript copy number							Slope[c]	Efficiency (%)[d]
	7.5×10^0	7.5×10^1	7.5×10^2	7.5×10^3	7.5×10^4	7.5×10^5	7.5×10^6		
SARS1									
RNA transcript alone	Neg	38.65±1.48	34.25±0.57	31.1±0.14	27.5	24.2	20.55±0.07	–3.55	91.1
RNA transcript + extract[e]	Neg	38.05±0.92	34.85±0.21	31.55±0.07	27.75±0.07	24.4	20.6	–3.49	93.3
	2×10^0	2×10^1	2×10^2	2×10^3	2×10^4	2×10^5	2×10^6		
SARS2									
RNA transcript alone	35.4±0.57	32.1±0.14	29.45±0.64	26.15±0.07	22.9±0.14	19.4	16.35±0.07	–3.21	104.9
RNA transcript + extract	Neg	34.55±1.91	29.2±0.28	26.2	23.1	19.6±0.14	16.6	–3.48	93.9
SARS3									
RNA transcript alone	39.3	36.2±0.42	32.8	29.1±0.14	25.9	22.15±0.07	19.2	–3.39	97.1
RNA transcript + extract	40.3	36.2±0.28	33.4±0.28	29.9±0.21	26.05±0.07	22.55±0.21	19.65±0.21	–3.42	96.1

[a]PCR, polymerase chain reaction; CT, threshold cycle number.; neg, negative.
[b]Values shown are mean of triplicate samples ± standard deviations.
[c]Slope determined from the formula: Y = Y intercept – slope $\log_{10}$. Slopes calculated for SARS1 (7.5×10^6 to 7.5×10^1); SARS2 (2×10^6 to 2×10^1); SARS3 (2×10^6 to 2×10^0).
[d]Efficiency = $[10^{(-1/\text{slope})}] - 1$.
[e]Reactions performed in presence of pooled total nucleic acid extract from 20 human respiratory specimens.

as human and nonhuman primate cell lines were tested. No positive reactions were obtained with any of the primer and probe sets.

Evaluation with Clinical Specimens

The real-time RT-PCR assay was used to test 14 clinical specimens (including throat swab [2 specimens], sputum [1 specimen], throat wash [5 specimens], and lung autopsy tissues [6 specimens]) from 10 patients with laboratory confirmed SARS-CoV infection (Table 5). Assay results were positive with all specimens for all three primer/probe sets. An additional, 326 respiratory specimens collected during the course of the outbreak from 236 suspected U.S. SARS patients who were serologically negative for SARS-CoV infection were also negative by the real-time RT-PCR.

Discussion

In response to the SARS outbreak, we developed a real-time RT-PCR assay based on multiple primer and probe sets designed to different genomic targets to facilitate sensitive and specific detection of SARS-CoV in clinical specimens. A potential detection limit of <10 transcript copies per reaction was achieved with greater relative sensitivity than cell culture isolation or conventional RT-PCR. The potential for quantitation over a wide dynamic range (at least 6 logs) was demonstrated with low intra- and interassay variability and limited inhibition from exogenous nucleic acid extract from respiratory secretions. The increased sensitivity of the real-time RT-PCR assay over cell culture and conventional RT-PCR methods may aid detection of the virus at earlier stages of infection, when the virus is present at low titer in respiratory secretions (8). In addition, by eliminating the need for postamplification product processing, the real-time RT-PCR format permitted shortened turnaround time for reporting results, which proved critical during the SARS outbreak.

Table 4. Comparison of real-time RT-PCR assay with culture and conventional RT-PCR[a]

SARS-CoV dilution[b]	Conventional RT-PCR	Real-time RT-PCR		
		SARS1	SARS2	SARS3
10^{-4}	3/3[c]	3/3	3/3	3/3
10^{-5}	3/3	3/3	3/3	3/3
10^{-6}	3/3	3/3	3/3	3/3
10^{-7}	3/3	3/3	3/3	3/3
10^{-8}	0/3	3/3	3/3	3/3
10^{-9}	0/3	0/3	1/3	0/3
10^{-10}	0/3	0/3	0/3	0/3

[a]RT-PCR, reverse transcription–polymerase chain reaction; SARS-CoV, severe acute respiratory syndrome–associated coronavirus.
[b]Serial 10-fold dilution of SARS-CoV stock culture containing 1×10^7 PFUs/mL.
[c]Number of positive results divided by the number of replicates tested.

Although real-time RT-PCR offers clear advantages over more conventional RT-PCR formats, assay results must still be interpreted with caution. For example, the effectiveness of RT-PCR for detection of SARS-CoV in clinical specimens has been shown to be greatly influenced by the quantity, type, and timing of specimen collection (8,17). False-negative results due to poor quality nucleic acid or presence of RT-PCR inhibitors can also be a concern. We addressed this by simultaneously testing for the human RNase P gene, which should be present in all adequately collected samples. False-negative results could also potentially arise from mutations occurring in the primer and probe target regions in the SARS-CoV genome. We addressed this by including multiple genetic targets in our assay and by carefully comparing our primer and probe sequences against published sequences of SARS-CoV as they became available. To avoid false-positive results, meticulous care was taken to prevent introduction of contaminating viral RNA or previously amplified DNA during preparation of the nucleic acid extracts and amplification reactions. In addition, all RT-PCR–positive specimens were retested from a second, unopened sample aliquot and confirmed in a second laboratory by using a real-time assay based on different genetic targets.

Table 5. Results of real-time RT-PCR assay with specimens from patients with laboratory-confirmed SARS-CoV infection

Case ID	Location	Specimen ID	Specimen	Serology	Vero E6 culture	Conventional RT-PCR[b]	Real-time RT-PCR C_T[c] values			
							SARS1	SARS2	SARS3	RNase P
05078	Toronto	2003756523	Lung, RM	N/A	–	+	24.2	21.6	23	23.9
		2003756525	Lung, RU		–	+	24.9	21.5	23	23.7
05077	Thailand	2003756502	Throat swab	+	+	+	37.5	36.2	39.8	29.3
05000	Hong Kong	2003757035	Lung, RU	+	–	+	26.7	22.6	24.1	24.7
		2003757036	Lung, LU		–	+	27.2	24.9	26.5	26
		2003757037	Lung, RM		–	+	34.9	37.5	31.9	27.4
		2003757038	Lung, LL		–	+	29.6	27	28.6	24.5
00220	Utah, USA	2003757508	Sputum	+	+	+	24.7	23	24.8	30.6
05001	Vietnam	2003757190	Throat wash	+	+	+	23.7	22.4	24.1	30.1
05008	Vietnam	2003757229	Throat wash	+	–	+	35.5	35.5	36.7	30
05010	Vietnam	2003757239	Throat wash	+	–	+	31.1	29.3	31.5	34.2
05013	Vietnam	2003757251	Throat wash	+	–	+	29.5	28.4	30.3	28.8
05017	Vietnam	2003757268	Throat wash	+	+	+	26	24.7	26.4	27.9
05316	Vietnam	2003759760	Throat swab	N/A	+	N/A	25	25.3	28.2	28

[a]RT-PCR, reverse transcription–polymerase chain reaction; SARS-CoV, severe acute respiratory syndrome–associated coronavirus; CT, threshold cycle number; RM, right middle; RU, right upper; LU, left upper; LL, left lower; N/A, not applicable.
[b]Ref. 5.
[c]Values shown mean of duplicate values.

In conclusion, our real-time RT-PCR assay permitted rapid, sensitive, and specific detection of SARS-CoV in clinical specimens and provided needed diagnostic support during the recent SARS outbreak. Widely deploying this assay through the LRN will enhance our ability to provide a rapid response in the event of the possible return of SARS.

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Interferon-β 1a and SARS Coronavirus Replication

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A global outbreak of severe acute respiratory syndrome (SARS) caused by a novel coronavirus began in March 2003. The rapid emergence of SARS and the substantial illness and death it caused have made it a critical public health issue. Because no effective treatments are available, an intensive effort is under way to identify and test promising antiviral drugs. Here, we report that recombinant human interferon -β 1a potently inhibits SARS coronavirus replication in vitro.

The recent global outbreak of severe acute respiratory syndrome (SARS) has quickly gained notoriety as a newly emerging infectious disease. The etiologic agent was identified as a coronavirus (SARS-CoV) that is not closely related to any of the previously characterized coronaviruses (1,2). As of September 26, 2003, a total of 8,098 probable cases of SARS have occurred with 774 deaths.

No antiviral treatments are currently available against SARS-CoV. SARS cases have been treated symptomatically according to the severity of the illness. A treatment protocol consisting of antibacterial agents and a combination of ribavirin and methylprednisolone was recently proposed. However, the therapeutic value of ribavirin remains uncertain because it has no activity against SARS-CoV in vitro. Molecular modeling studies suggest that rhinovirus $3C^{pro}$ inhibitors may be useful for SARS therapy, but results of recent in vitro testing of the lead molecule, AG7088, were negative (3).

Previous studies showed that some coronaviruses, including avian infectious bronchitis virus, murine hepatitis virus, and human coronavirus 229E, are susceptible to type I interferons in vitro or in vivo (4–7). Therefore, we evaluated the in vitro efficacy of a recombinant human type I interferon (IFN), IFN-β 1a (Serono International, Geneva, Switzerland) against three different isolates of SARS-CoV (Tor2 and Tor7 and Urbani) using yield reduction assays. The IFN-β 1a preparation employed in this study was selected because it is currently used as part of the most effective treatment regimen for relapsing forms of multiple sclerosis (8), and more importantly, because it was shown to have antiviral activity (as measured in a vesicular stomatitis virus cytopathic assay system) 14 times greater than the currently available treatment using IFN-β 1b (9).

In the current study, Vero E6 cells were treated with concentrations (5,000 to 500,000 IU/mL) of IFN-β 1a either 24 h before or 1 h after inoculation with the SARS-CoV (multiplicity of infection 0.1 PFU/cell), and monitored for cytopathic effect and production of infectious SARS-CoV at 24, 48, and 72 h postinfection. Inhibition of the SARS-CoVs by IFN-β 1a was dependent on both time of drug administration and time of culture sampling after SARS-CoV infection. Production of infectious SARS-CoV was potently inhibited (≥99.5% or 2.00 $\log_{10}$ PFU/mL) at 24 h postinfection by pretreatment of Vero E6 cells with IFN-β 1a at all concentrations tested (Figure 1). By 72 h postinfection, inhibition of SARS-CoV production by IFN-β 1a had declined for all three SARS-CoVs, with inhibition (≥70%) being detected in the Tor7 (Figure 1) and Urbani isolates (data not shown). IFN-β 1a was somewhat less effective at inhibiting SARS-CoV replication when employed after infection of cultures (Figure 1). Nonetheless, production of infectious SARS-CoVs was considerably reduced (≥90% or 1.00 $\log_{10}$ PFU/mL) at 24 and 48 h postinfection. Protection of Vero E6 monolayers against SARS-CoV–induced cytopathic effects by preinfection or postinfection treatment with IFN-β 1a was dramatic, even at 72 h postinfection (Figure 2). Additional concentrations of IFN-β 1a (0.5–5,000 IU/mL) were tested to determine the 50% inhibitory concentration (IC_{50}). Pretreatment of Vero E-6 cells with concentrations as low as 50 IU/mL, or posttreatment of cells with concentrations at 500 IU/mL, provided a 50% reduction with the Tor2 isolate at 24 h postinfection.

Faced with a burgeoning epidemic of SARS cases and a lack of effective treatment options, identifying compounds with antiviral activity that could be potential therapeutics has become a high priority. Our report suggests

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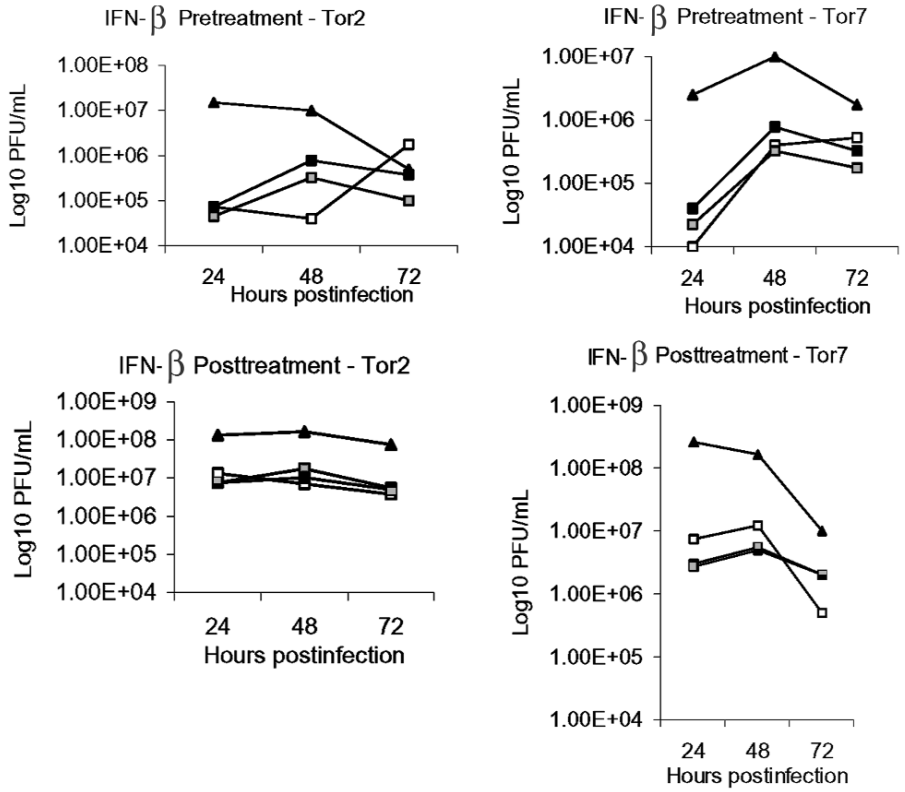

Figure 1. Interferon (IFN)-β 1a inhibition of SARS-CoV replication in Vero E6 cells. Top panels, Vero E6 cells were incubated in the absence (-▲-) or presence of IFN-β 1a added 24 h before infection with the Tor2 (left) or Tor7 (right) isolate of SARS Co-V. Bottom panels, Vero E6 cells were incubated in the absence (-▲-) or presence of IFN-β 1a added 1 h after infection with the Tor2 (left) or Tor7 (right) isolate of SARS Co-V. Three concentrations of IFN-β 1a were employed for both studies: 5,000 IU/mL (-❑-), 50,000 IU/mL (-■-), 500,000 IU/mL (-■-) Samples of overlying media were collected at 24, 48, and 72 h postinfection and analyzed by plaque assay on Vero E6 cells.

that IFN-β 1a may be effective as a treatment for SARS-CoV infections. As noted above, IFN-β 1a is currently being used for a variety of clinical indications, including multiple sclerosis, and has shown dose-dependent efficacy in several clinical trials. Importantly, IFN-β 1a exhibited potent antiviral activity at doses that have already been shown to have acceptable safety profiles in animals (10). Thus, we report the identification of a compound that may be suitable for rapid development as a treatment for SARS-CoV infection.

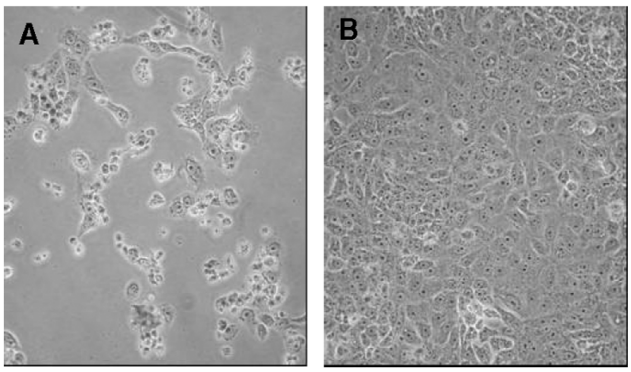

Figure 2. Interferon (IFN)-β 1a inhibition of SARS-CoV cytopathicity in Vero E6 cells. Vero E6 cells were infected with the Tor2 isolate of SARS-CoV and incubated for 72 h in the absence (left panel) or presence (right panel) of 500,000 IU of recombinant human IFN-β 1a. Cell rounding and detachment were prominent in the absence of IFN-β 1a. Minimal cell rounding or death was noted in the intact monolayer at 72 h postinoculation in the presence of IFN-β 1a (note: IFN-β 1a administered 1 h postinfection).

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Ultrastructural Characterization of SARS Coronavirus

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Severe acute respiratory syndrome (SARS) was first described during a 2002–2003 global outbreak of severe pneumonia associated with human deaths and person-to-person disease transmission. The etiologic agent was initially identified as a coronavirus by thin-section electron microscopic examination of a virus isolate. Virions were spherical, 78 nm in mean diameter, and composed of a helical nucleocapsid within an envelope with surface projections. We show that infection with the SARS-associated coronavirus resulted in distinct ultrastructural features: double-membrane vesicles, nucleocapsid inclusions, and large granular areas of cytoplasm. These three structures and the coronavirus particles were shown to be positive for viral proteins and RNA by using ultrastructural immunogold and in situ hybridization assays. In addition, ultrastructural examination of a bronchiolar lavage specimen from a SARS patient showed numerous coronavirus-infected cells with features similar to those in infected culture cells. Electron microscopic studies were critical in identifying the etiologic agent of the SARS outbreak and in guiding subsequent laboratory and epidemiologic investigations.

A large outbreak of severe pneumonia associated with human deaths occurred in late 2002 in Guangdong Province, China. Beginning in late February 2003, a similar illness was reported concurrently in Vietnam, Hong Kong, Canada, Singapore, and other countries (1,2). The disease, now known as severe acute respiratory syndrome (SARS), causes an influenzalike illness with fever, cough, dyspnea, and headache. Person-to-person transmission, combined with international travel of infected persons, accelerated the worldwide spread of the illness. By the time the outbreak was contained, 8,098 probable cases, resulting in 774 deaths, were identified in 29 countries (3).

A global network of 11 laboratories was established by the World Health Organization to identify the causal agent (4). Initial clinical and laboratory results focused on several known agents of respiratory illness, including human metapneumovirus, influenza virus, and *Chlamydia* (4,5). A virus was isolated from the oropharynx of a SARS patient and identified by morphologic characteristics as belonging to the family *Coronaviridae* (6–8); however, coronaviruses had not been a prime consideration in the differential diagnosis since they rarely cause lower respiratory tract infections in humans (9–11). Electron microscopic findings thus shifted the focus of the laboratory investigation toward verification of these observations. These findings subsequently were corroborated by immunohistochemical, immunofluorescent, and serologic assays, by additional culture isolates, and by a variety of molecular approaches, including reverse transcription–polymerase chain reaction, microarray analysis, and sequencing (5–7,12,13). As a result of those studies, the SARS-associated coronavirus (SARS-CoV) is now recognized as the etiologic agent of this syndrome.

We present here the ultrastructural features of SARS-CoV in cell culture and in a bronchial alveolar lavage (BAL) specimen. Viral immunogold labeling and ultrastructural in situ hybridization (ISH) were used to further analyze the morphogenesis of this newly emergent virus.

Methods

Infected and uninfected Vero E6 cells were harvested 3–5 days after inoculation, inactivated by fixation and gamma irradiation (2×10^6 rad), and processed for standard, immunolabeling electron microscopy (IEM) or ISH EM as previously described (6,14). For standard EM, glutaraldehyde- and osmium tetroxide–fixed specimens were embedded in Epon-substitute and Araldite (Ted Pella, Inc., Redding, CA) and sections were stained with uranyl acetate and lead citrate. Some infected and uninfected cultures were treated with 5% tannic acid solution before being embedded for standard EM (15). Specimens prepared for IEM and ISH assays were fixed in paraformaldehyde and glutaraldehyde and embedded in LR White resin (Ted Pella, Inc.), and sections were collected on nickel mesh grids.

A BAL specimen was obtained from a 47-year-old man within the first week of the onset of symptoms. A portion of the specimen was centrifuged at 2,000 rpm for 10 min, and the pellet was processed for standard EM.

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IEM and ISH assays were performed essentially as described for Nipah virus (14). In brief, for IEM assays, sections were reacted with hyperimmune mouse ascitic fluid raised against SARS-CoV and then with a goat anti-mouse antibody conjugated to 12-nm colloidal gold particles (Jackson ImmunoResearch Laboratories, Inc., West Grove, PA). Negative-sense riboprobes for the ultrastructural ISH assays were prepared as previously described (16,17). Riboprobes were directed against the nucleocapsid or polymerase protein portions of the SARS-CoV genome (Table) and incorporated digoxigenin-11-dUTP. Because of the nested set structure of the coronavirus genomic RNA (genRNA) and messenger RNAs (mRNAs), the nucleocapsid riboprobe would detect all viral RNAs (18). Sections were reacted with a pool of nucleocapsid and polymerase probes and then with a sheep anti-digoxigenin antibody conjugated to 6-nm colloidal gold particles (Electron Microscopy Sciences, Hatfield, PA). To obtain negative controls, we performed both assays with uninfected Vero E6 cells, and infected cells were reacted with an unrelated antibody and probe for IEM and ISH procedures, respectively.

Table. Riboprobes used for in situ hybridization studies of severe acute respiratory-syndrome-associated coronavirus[a]

Gene	Nucleotide positions	Riboprobe size (nucleotides)
Polymerase	15,250–15,755	325
Nucleocapsid	29,083–29,708	625

[a]GenBank accession no. AY27874

Results

Ultrastructural Characteristics of SARS-CoV–Infected Culture Cells

The morphologic features of SARS-CoV isolates were similar to those of other members of the family *Coronaviridae.* Multinucleated syncytial cells were occasionally seen. Nascent particles were formed by the juxtaposition of viral nucleocapsids along cytoplasmic membranes of the budding compartment (the membrane region between the rough endoplasmic reticulum and the Golgi complex) or occasionally on the membranes of the rough endoplasmic reticulum that form the outer layer of the nuclear membrane. Virions acquired an envelope by budding into the cisternae and formed mostly spherical, sometimes pleomorphic, particles that averaged 78 nm in diameter (Figure 1A). Cross-sections through the helical

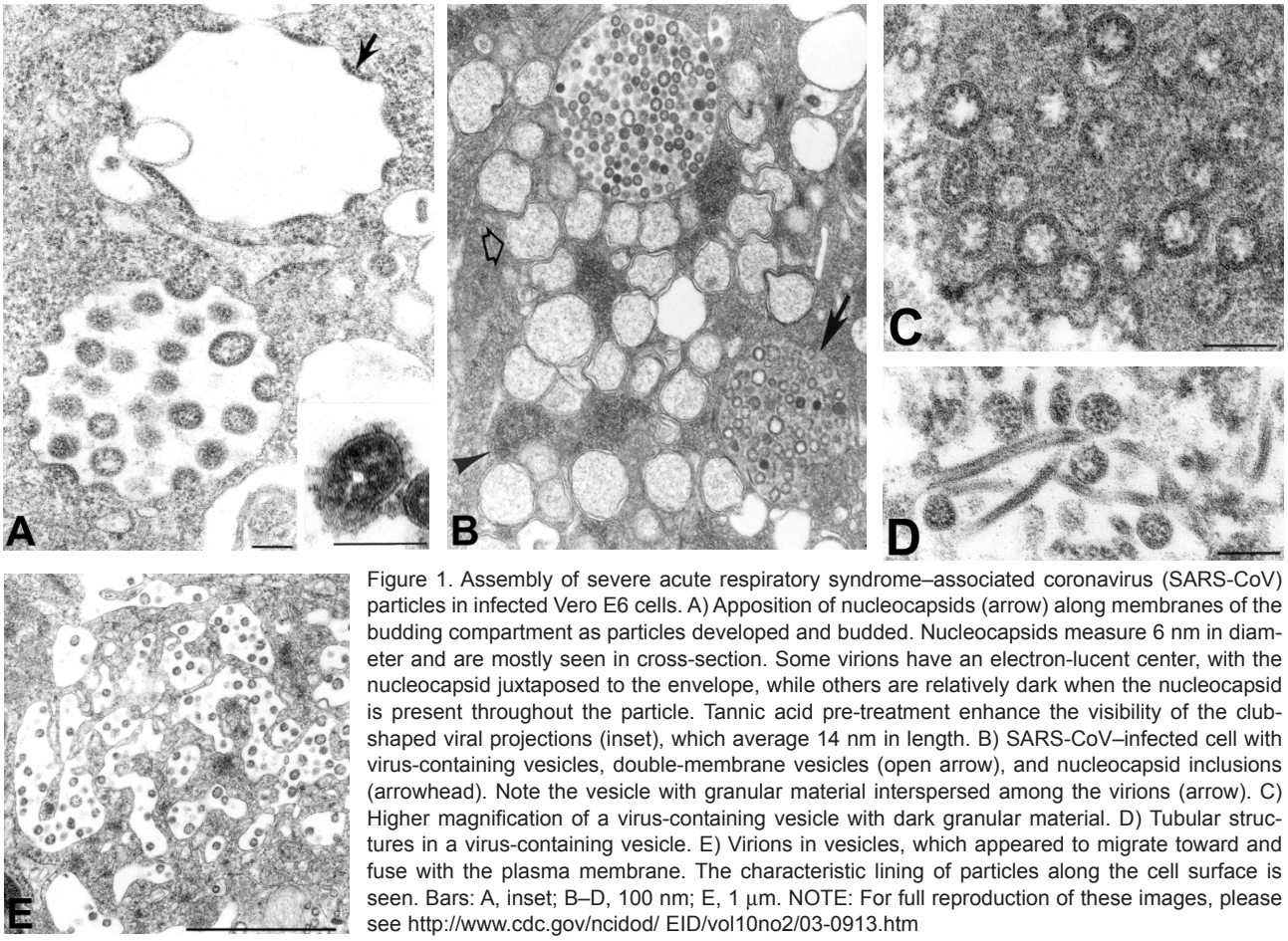

Figure 1. Assembly of severe acute respiratory syndrome–associated coronavirus (SARS-CoV) particles in infected Vero E6 cells. A) Apposition of nucleocapsids (arrow) along membranes of the budding compartment as particles developed and budded. Nucleocapsids measure 6 nm in diameter and are mostly seen in cross-section. Some virions have an electron-lucent center, with the nucleocapsid juxtaposed to the envelope, while others are relatively dark when the nucleocapsid is present throughout the particle. Tannic acid pre-treatment enhance the visibility of the club-shaped viral projections (inset), which average 14 nm in length. B) SARS-CoV–infected cell with virus-containing vesicles, double-membrane vesicles (open arrow), and nucleocapsid inclusions (arrowhead). Note the vesicle with granular material interspersed among the virions (arrow). C) Higher magnification of a virus-containing vesicle with dark granular material. D) Tubular structures in a virus-containing vesicle. E) Virions in vesicles, which appeared to migrate toward and fuse with the plasma membrane. The characteristic lining of particles along the cell surface is seen. Bars: A, inset; B–D, 100 nm; E, 1 μm. NOTE: For full reproduction of these images, please see http://www.cdc.gov/ncidod/ EID/vol10no2/03-0913.htm

nucleocapsid were seen apposed to the viral envelope, and the interior of the particles was usually electron-lucent. Surface projections were faint in standard thin-section preparations and could be better visualized by using a tannic acid treatment (Figure 1A, inset).

Virus particles were seen in membrane-bound vesicles, either as single particles or as groups in enlarged vesicles. In some of these vesicles, dense, granular material was seen interspersed between the virions (Figure 1B, C). Tubular structures, averaging 20 nm in diameter, were seen within some virion-containing vesicles (Figure 1D). The vesicles appeared to migrate toward the cell surface and fuse with the plasma membrane, releasing the viral particles (Figure 1E). Many of the particles adhered to the plasma membrane, creating a knob-like appearance on the surface of the cells.

Viral proteins and RNA were detected in virions by IEM and ISH (Figure 2A,B), and in association with double-membrane vesicles (Figure 3A,B), nucleocapsid inclusions, and large granular areas of cytoplasm (Figure 4C,D). Double-membrane vesicles have been noted in other coronavirus-infected cells (19,20) and consist of cytoplasmic vesicles with two tightly apposed membranes (Figure 1B). In contrast, double-membrane vesicles in SARS-CoV–infected Vero E6 cells typically were composed of accumulations of multiple single-membrane vesicles enclosed within an outer membrane (Figure 3C), and virus particles were sometimes located between the two membranes (Figure 3D). Many double-membrane vesicles contained diffuse, granular material. Cytoplasmic inclusions of darkly staining viral nucleocapsids were mostly found in association with virus-containing vesicles or double-membrane vesicles (Figures 1B and 3D). Large, ill-defined areas of cytoplasm, containing ribosomelike and filamentous structures and devoid of other organelles, were noted in some SARS-CoV–infected cells (Figure 4A,B). These areas strongly labeled for viral proteins and RNA (Figure 4C,D), with IEM and ultrastructural ISH assays. No antigens or RNA were detected by reacting hyperimmune mouse ascitic fluid or riboprobes with uninfected Vero E6 cells or by reacting an unrelated hyperimmune mouse ascitic fluid or riboprobe with SARS-CoV–infected cells.

Finally, as has been reported previously for other coronaviruses, SARS-CoV–infected cells also contained tubuloreticular structures, with virions sometimes forming along the membranes (Figure 3C). The tubuloreticular structures were often found in close association with double-membrane vesicles.

Ultrastructural Characteristics of SARS-CoV–Infected BAL Specimen

A number of coronavirus-infected cells were seen within a BAL specimen from a SARS patient (Figure 5A,B). Virus particles budded into, and were associated with, vesicles, and extracellular virions covered the exterior surface of the cells. Areas of double-membrane vesicles containing a diffuse granular material were also seen.

Discussion

During the global SARS outbreak of 2002 to 2003, a virus was isolated from human patients and identified by EM as belonging to the family *Coronaviridae* (6,7). Detailed studies described here on the morphogenesis of

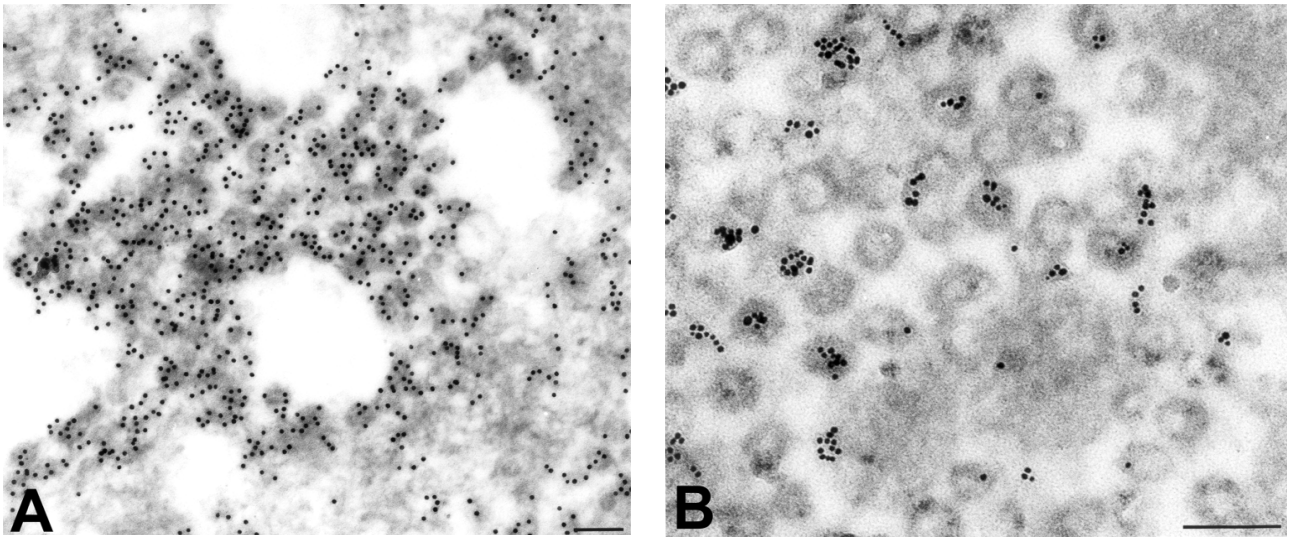

Figure 2. Detection of viral proteins and viral RNA associated with intracytoplasmic virions. A) Immunogold labeling of viral proteins by using hyperimmune mouse ascitic fluid directed against severe acute respiratory syndrome–associated coronavirus (12 nm gold). B) Ultrastructural in situ hybridization detection of viral RNA by using a pool of polymerase and nucleocapsid riboprobes (6 nm gold). Bars, 100 nm.NOTE: For full reproduction of these images, please see http://www.cdc.gov/ncidod/EID/vol10no2/03-0913.htm

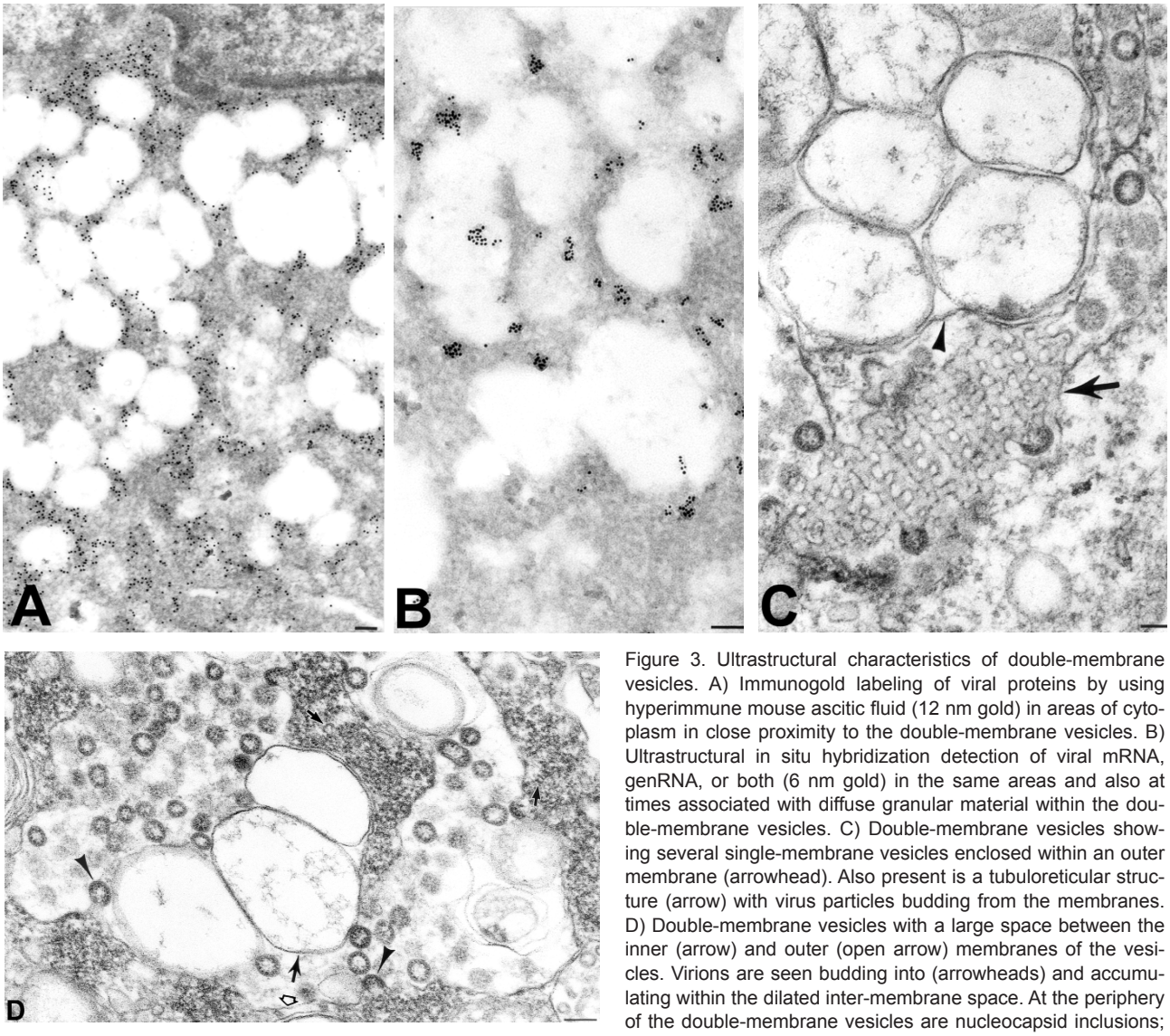

Figure 3. Ultrastructural characteristics of double-membrane vesicles. A) Immunogold labeling of viral proteins by using hyperimmune mouse ascitic fluid (12 nm gold) in areas of cytoplasm in close proximity to the double-membrane vesicles. B) Ultrastructural in situ hybridization detection of viral mRNA, genRNA, or both (6 nm gold) in the same areas and also at times associated with diffuse granular material within the double-membrane vesicles. C) Double-membrane vesicles showing several single-membrane vesicles enclosed within an outer membrane (arrowhead). Also present is a tubuloreticular structure (arrow) with virus particles budding from the membranes. D) Double-membrane vesicles with a large space between the inner (arrow) and outer (open arrow) membranes of the vesicles. Virions are seen budding into (arrowheads) and accumulating within the dilated inter-membrane space. At the periphery of the double-membrane vesicles are nucleocapsid inclusions; arrows point to discernable nucleocapsids (small arrows). Bars, 100 nm. NOTE: For full reproduction of these images, please see http://www.cdc.gov/ncidod/EID/vol10no2/03-0913.htm

the SARS-CoV by thin-section EM found many characteristics previously described for coronaviruses (19,21,22). Virus particles formed upon membranes of the "budding compartment," a term used to describe the continuous membrane system from the rough endoplasmic reticulum to the Golgi complex (23,24). Virions accumulated in dilated vesicles that appeared to migrate to the cell surface where the virus particles were released or remained adherent to the plasma membrane. Additional cytoplasmic structures associated with coronavirus infections included nucleocapsid inclusions and double-membrane vesicles, which have been proposed as the replication complex for coronaviruses (20) and arteriviruses (25), a closely related virus family that, in addition to coronaviruses, is a member of the order Nidovirales. IEM and ultrastructural ISH assays detected viral proteins and mRNA or genRNA associated with virions, double-membrane vesicles, and nucleocapsid inclusions. Coronaviruses are known to synthesize a nested set of subgenomic mRNAs (26), such that the nucleocapsid riboprobe used here allowed detection of all viral mRNAs in addition to genRNA. Indeed, considerable amounts of RNAs were detected in the ultrastructural ISH assays performed on SARS-CoV–infected cells.

As has been reported for other coronaviruses, additional cytoplasmic features were associated with SARS-CoV–infected cells. Tubular structures were occasionally seen within virus-containing vesicles (27,28); and cytoplasmic tubuloreticular structures, known to occur with

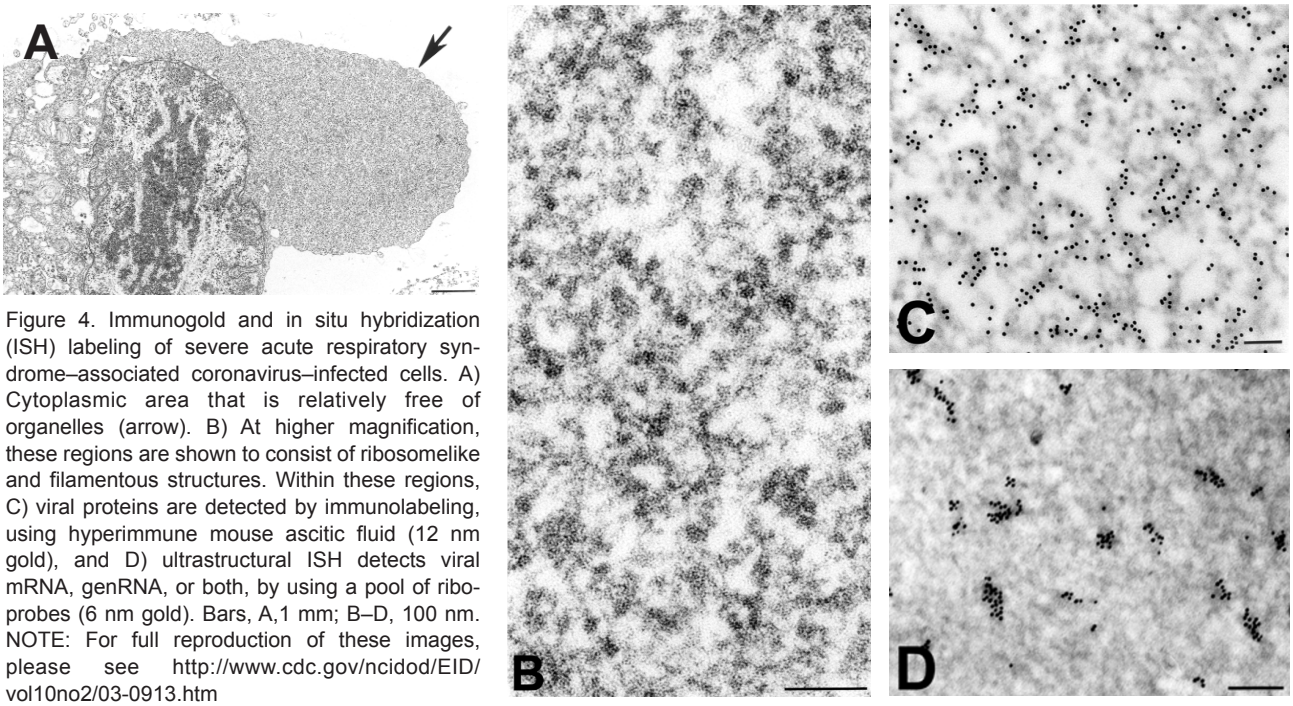

Figure 4. Immunogold and in situ hybridization (ISH) labeling of severe acute respiratory syndrome–associated coronavirus–infected cells. A) Cytoplasmic area that is relatively free of organelles (arrow). B) At higher magnification, these regions are shown to consist of ribosomelike and filamentous structures. Within these regions, C) viral proteins are detected by immunolabeling, using hyperimmune mouse ascitic fluid (12 nm gold), and D) ultrastructural ISH detects viral mRNA, genRNA, or both, by using a pool of riboprobes (6 nm gold). Bars, A,1 mm; B–D, 100 nm. NOTE: For full reproduction of these images, please see http://www.cdc.gov/ncidod/EID/vol10no2/03-0913.htm

numerous other infections (29), were also found. Large granular areas of cytoplasm, relatively devoid of organelles and containing viral proteins and RNA, were noted in SARS-CoV–infected cells; such features have not been described previously for coronaviruses. While the role of these cytoplasmic areas is unclear, the close proximity of cellular ribosomes with viral proteins and RNA suggests that they may be viral translation centers. Future ultrastructural ISH and IEM studies to characterize these areas, using riboprobes and monoclonal antibodies to specific SARS-CoV genes and gene products, should help clarify this issue.

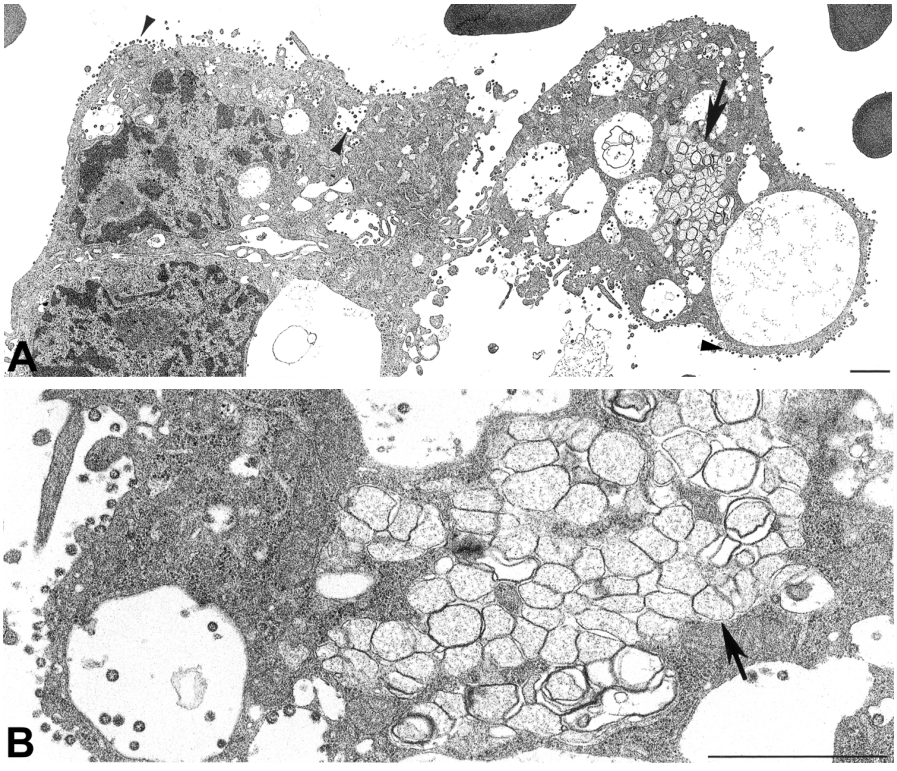

Figure 5. Ultrastructural characteristics of a bronchial alveolar lavage (BAL) from a patient with severe acute respiratory syndrome. A) Infected cells showing numerous cytoplasmic and extracellular virions (arrowheads). Note the region of double-membrane vesicles (arrow), a common feature of coronavirus-infected cells. B) At higher magnification, double-membrane vesicles (arrow) are shown to contain diffuse, granular material. Bars, 1 μm. NOTE: For full reproduction of these images, please see http://www.cdc.gov/ncidod/EID/ vol10no2/03-0913.htm

Many of these ultrastructural findings were also observed in a BAL specimen from a SARS patient (Figure 5B) (6). Characteristic virions in vesicles and lining the cell surface and the presence of double-membrane vesicles provided clear evidence of a coronavirus infection and suggested that viral replication was occurring in the lower airways early in the course of infection. EM examination of BAL specimens may prove to be a useful tool in the diagnosis of SARS-CoV, analogous to the use of BAL specimens to diagnose influenza infections. Recent studies have reported finding coronavirus particles in lung and gastroenteric tissues of SARS patients and experimentally infected macaques (7,30–33), although the viral nature of these structures has not been confirmed by IEM or ultrastructural ISH assays. Coronavirus particles may be confused morphologically with other nonviral structures routinely found in cells, including coated vesicles, multivesicular bodies, perichromatin granules, glycocalyceal bodies, and cellular projections (see 29). Therefore, a cautious approach is advisable when examining clinical specimens.

The SARS outbreak is a prime example of an emerging infectious disease that can rapidly and easily spread, reaching global proportions. With SARS, as with previous investigations of outbreaks involving such viruses as Ebola (34–36), Hendra (37), Nipah (38), and more recently, monkeypox (39), EM played an essential role in determining the specific virus family of the pathogen involved. In all of these cases, tissue culture amplification of a virus isolate facilitated the ultrastructural examination. Thus, traditional microbiologic and EM approaches proved pivotal in determining the etiologic agents, thereby guiding subsequent laboratory and epidemiologic investigations.

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Combining Clinical and Epidemiologic Features for Early Recognition of SARS

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Early recognition and rapid initiation of infection control precautions are currently the most important strategies for controlling severe acute respiratory syndrome (SARS). No rapid diagnostic tests currently exist that can rule out SARS among patients with febrile respiratory illnesses. Clinical features alone cannot with certainty distinguish SARS from other respiratory illnesses rapidly enough to inform early management decisions. A balanced approach to screening that allows early recognition of SARS without unnecessary isolation of patients with other respiratory illnesses will require clinicians not only to look for suggestive clinical features but also to routinely seek epidemiologic clues suggestive of SARS coronavirus exposure. Key epidemiologic risk factors include 1) exposure to settings where SARS activity is suspected or documented, or 2) in the absence of such exposure, epidemiologic linkage to other persons with pneumonia (i.e., pneumonia clusters), or 3) exposure to healthcare settings. When combined with clinical findings, these epidemiologic features provide a possible strategic framework for early recognition of SARS.

In November 2002, clusters of a highly transmissible and severe atypical pneumonia began appearing among residents of the Guangdong Province of China. These patients are now believed to have been the first persons with severe acute respiratory syndrome (SARS), a previously undescribed respiratory illness now known to be caused by a novel coronavirus (SARS-CoV) (1–4). These original clusters marked the beginning of an outbreak that spread rapidly around the globe, resulting in 8,098 reported cases from 32 countries and a case-fatality rate of 9.6% (5). On July 5, 2003, the World Health Organization (WHO) announced that all known person-to-person transmission of SARS-CoV had ceased (6). The cause for the decline in cases is not yet fully understood, but SARS-CoV may still possibly exist within either an animal or a human reservoir and cause future outbreaks (4). Clinicians and public health agencies must be prepared for the possible reappearance of SARS.

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Although many unanswered questions remain regarding the epidemiology of SARS, simple infection control measures can dramatically reduce transmission of SARS-CoV (7–10). In every region in which major outbreaks were reported, a substantial proportion of cases resulted from delays in clinical recognition and isolation of SARS patients after they were admitted into the healthcare system (8,9,11–13). Studies of transmission in Hong Kong, Singapore, and Ontario, Canada, suggest that early case detection will be a critical component in controlling future outbreaks of SARS (10,14–16).

Currently, no rapid diagnostic tests are widely available to rule out SARS. Because the early clinical features can be similar to those of other bacterial and viral infections, rapid recognition of SARS patients is likely to be particularly challenging in the context of seasonal outbreaks of other respiratory illnesses. The need for distinguishing patients with SARS from those with more common and benign illnesses presents clinicians with a diagnostic dilemma; screening methods that are not sufficiently sensitive may result in delays in recognition and uncontrolled transmission of SARS, while nonspecific screening methods could result in unnecessary isolation of large numbers of persons, rapidly overburdening the already limited resources of both the healthcare and public health systems.

A balanced approach to early recognition of SARS will require clinicians to look not only for suggestive clinical features but also for epidemiologic clues that suggest SARS-CoV infection. We provide a possible framework that combines epidemiologic features and clinical findings to formulate strategies for early recognition of SARS.

Clinical Description of SARS

Clinical Signs and Symptoms

The median incubation period for SARS appears to be approximately 4–6 days; most patients become ill within 2 to 10 days after exposure (8,12,17,18). Some evidence suggests that the incubation period may be as long as 14 days in some persons (17).

The most common initial symptom is fever, often accompanied by headache, myalgia, malaise, chills, and rigor (1,11,17–22). In some patients, headache, myalgia, and malaise precede the onset of fever by up to 1 day, and fever may have resolved by the time respiratory symptoms appear (1,18,19,22). Respiratory symptoms typically do not begin until 2–7 days after illness onset, although they are among the initial symptoms in up to 30% of patients (1,18–20). The most common respiratory complaints are lower respiratory tract symptoms, including nonproductive cough and dyspnea; productive cough is reported in up to 25% of patients (1,11,17–22). In some series, <10% of patients reported upper respiratory complaints (18,20,23), but in others the reported prevalence of rhinorrhea or sore throat is as high as 25% among patients with SARS (11,17,19). The prevalence of gastrointestinal symptoms has varied by report, but nausea, vomiting, diarrhea, or a combination of these symptoms has been reported in up to 25% of patients with SARS at the time of initial evaluation (1,11,17–22,24). In one series, diarrhea developed in 73% of patients at some point in the course of illness (22). Fever and diarrhea have been the dominant initial symptoms in some patients (13). Asymptomatic infection with SARS-CoV appears to be uncommon (25,26).

Elderly patients and those with underlying chronic illnesses such as renal failure may not have typical symptoms of SARS (12,13,27). For patients in this group who have strong epidemiologic risk factors for SARS, the diagnosis should be considered in almost any change in health status, even if the patients do not exhibit typical clinical features.

Physical Findings

Tachypnea, tachycardia, and hypoxemia have been reported in 40% to 75% of patients upon admission to the hospital (1,18–20) but may be less common in patients who are evaluated earlier in the course of illness as outpatients (21). Upon auscultation of the lungs, rales or rhonchi have been detectable in most patients in some series, and less commonly in others (18,20,21,28). Some researchers have observed a lack of lung sounds despite marked infiltration on chest radiography (21,28). As many as 15%–44% of patients may have a normal measured body temperature when first evaluated (18,19).

Laboratory Findings

Hematologic abnormalities are among the most consistent laboratory findings reported in patients with SARS; most patients have total leukocyte counts that are normal or slightly low, and 70%–95% of patients have lymphopenia (11,18–20,22,29). Platelet counts are mildly depressed in 30% to 50% of patients (11,19,22,29). Prolongation of the activated partial thromboplastin time can be observed in 40% to 60% of patients, but disseminated intravascular coagulation is uncommon (11,29).

Other common abnormal laboratory findings include elevated lactate dehydrogenase levels in 70% to 90% of patients (11,18,19), elevated alanine aminotransferase or aspartate aminotransferase levels in 20% to 30% (11,22), elevated creatine phosphokinase in 30% to 40% (11,22,30), and elevated C-reactive protein (1,31).

Radiographic Findings

While the full understanding of the spectrum of radiographic manifestations of SARS will require additional information, available data suggest that almost all reported patients with laboratory evidence of SARS-CoV infection have radiographic evidence of pneumonia documented at some point during their illness (19,21,31). Chest radiographs may be normal in up to 30% of patients with the clinical diagnosis of SARS at the time when first evaluated (18,22,32–34). In reports from China, radiographic changes consistent with pneumonia were detected in 67% to 80% of SARS patients by day 3 of illness, 97%–100% by day 7, and in 100% by day 10 (33,34). A lesion typically begins as an isolated focal lesion found in a peripheral location, often in the lower lobes. In 75% of patients, the lesions progress over several days to involve additional lobes or both lungs (32,34).

Computed tomography (CT) of the chest appears to be more sensitive than conventional chest radiography for detecting pneumonia; SARS patients who have normal chest radiographic findings early in their clinical course often have evidence of pneumonia by CT (11,35). Common CT findings are ground-glass opacification and a lower lobe and peripheral distribution (35).

Distinguishing SARS from Other Illnesses

As with other causes of bacterial and viral pneumonia, clinical findings in patients with SARS cannot accurately predict the causative agent. Further study is required to determine whether a constellation of clinical findings alone can be used to discriminate accurately between SARS and other (especially viral) respiratory illnesses. Many of the clinical and laboratory features of SARS are similar to those in other forms of viral pneumonia (28,36). Several clinical features, however, may be helpful in facilitating recognition of patients with SARS (Table 1).

Laboratory Tests for SARS-CoV

The main laboratory tests available to diagnose SARS-CoV infection are RNA detection through reverse transcriptase-polymerase chain reaction (RT-PCR) or real-time PCR and serologic testing for antibodies against SARS-CoV (1,2,22). None of these tests can be used reliably to detect the presence or absence of SARS-CoV infection at

the time of initial evaluation. RT-PCR and real-time PCR are insufficiently sensitive to reliably diagnose all persons with SARS when first evaluated; in one study, SARS-CoV was initially detected in nasopharyngeal samples by RT-PCR in 32% of patients and in 68% at day 14 after illness onset (22). PCR tests also can provide false-positive test results even in the most experienced laboratories, so their indiscriminant use for persons at low risk for SARS infection could result in a false diagnosis of SARS and unnecessarily initiating isolation and quarantine measures. Although antibodies can be detected in serologic assays starting at 10 to 14 days after illness onset (2,22), serologic tests cannot reliably rule out SARS-CoV infections until 28 days after onset of symptoms, when sensitivity is at least 93% (22).

While respiratory samples have been the most commonly used samples for virus detection, virus may be more readily detectable in serum earlier in the course of illness and in stool samples later in the course of illness (1,22) (Centers for Disease Control and Prevention [CDC], unpub. data). More research is needed to determine the optimal timing of sample collection, the duration of shedding, and the optimal type of sample.

Epidemiologic Features Important for Early Recognition of SARS

Given that no specific clinical or laboratory findings can with certainty distinguish SARS from other respiratory illnesses rapidly enough to inform early management decisions, epidemiologic features are critical to early recognition of SARS. Epidemiologic features that may be helpful in early recognition include a history of exposure to known SARS case-patients or SARS-affected areas, an epidemiologic linkage to a cluster of pneumonia cases, a history of travel to previously SARS-affected areas, and employment as a healthcare worker with direct patient care.

Epidemiologic Linkage to Cases or SARS-affected Areas

The predominant mode of transmission of SARS-CoV appears to be through large respiratory droplets or direct contact (7,8). This mode of transmission is consistent with the observation that most patients can be linked, either directly or indirectly, to persons with SARS or places where transmission is either suspected or documented (17,37). In the Toronto and Singapore outbreaks, >94% of case-patients had documented contact with a SARS patient or with a hospital ward where there was a known SARS patient (8,38). Therefore, determining if persons with symptoms compatible with SARS have an epidemiologic linkage either to other persons with known or suspected SARS or to places with known or suspected transmission of SARS-CoV is important.

Table 1.Common clinical features of severe acute respiratory syndrome (SARS)

Clinical feature	Common findings with SARS-associated coronavirus infection
Initial symptoms	Nonrespiratory prodrome lasting 2–7 days characterized by one or more of the following:
	Fever
	Rigors
	Headache
	Malaise
	Myalgia
	Diarrhea
	Respiratory phase beginning 2–7 days after onset characterized by:
	Nonproductive cough
	Dyspnea
	Absence of upper respiratory symptoms
Laboratory Findings	Normal or low total leukocyte cell count
	Lymphopenia
	Mildly depressed platelet count
	Elevated lactate dehydrogenase levels
	Elevated creatine phosphokinase levels
	Elevated transaminase levels
	Prolonged activated partial thromboplastin time
Radiographic Findings	Abnormal chest x-ray results in almost all patients by the second week of illness

Whether a history of travel to areas previously affected by SARS will be a useful epidemiologic clue for recognizing future outbreaks depends in part on whether SARS-CoV currently exists within a human or an animal reservoir. If the virus exists within a human reservoir, the virus could reemerge anywhere on the globe, although the areas of highest activity during the recent outbreaks are most likely to harbor persistent infection in humans. Alternatively, if SARS-CoV currently exists primarily within the animal reservoir from which it originated, future outbreaks may more likely originate in Southeast Asia. Given that China appears to have been the origin of the most recent outbreak (4,39) and neighboring areas are at greatest risk, persons traveling in Southeast Asia, especially in China, Hong Kong, and Taiwan, may be at increased risk for infection if SARS recurs.

Case Clustering

The major limitation of relying on linkage to settings of known transmission to identify persons at risk for SARS is identifying the first cases acquired in an area not previously known to have circulation of SARS-CoV. Because SARS-CoV infections tend to appear in clusters, one potential strategy for early recognition in such areas is to seek evidence for clustering of pneumonia cases. Early recognition of clusters requires clinicians evaluating patients with pneumonia to routinely seek a history of exposure to others with pneumonia.

Healthcare Association

Healthcare facilities have played a central role in the epidemiology of SARS. Persons who work in healthcare settings were among the earliest and most severely affected group in almost every major outbreak reported, particularly during the earliest phases of the outbreak (8,11,13). For example, in the Toronto and Singapore outbreaks, 43% and 41%, respectively, of the SARS cases occurred in healthcare workers (40). Therefore, atypical pneumonia among healthcare workers should raise the suspicion for SARS, particularly if there are multiple cases among healthcare workers in the same facility.

Combining Clinical and Epidemiologic Features

Since patients may transmit the virus early in the clinical course (8), the goal of diagnostic strategies should be to detect patients with SARS as early in the illness as possible to prevent potential transmission. A practical approach to evaluating patients with fever or respiratory symptoms is needed, which requires an assessment of the strength of the evidence of exposure to other SARS-CoV–infected persons. This assessment is directly related to the level of documented SARS activity in the surrounding community and the world.

Evaluating Patients in the Absence of Documented SARS Activity Anywhere in the World

In the absence of any documented SARS transmission worldwide, the overall likelihood that a given patient has SARS-CoV infection will be exceedingly low unless there are both typical clinical findings and some accompanying epidemiologic evidence for SARS-CoV infection. Therefore, one approach would be to consider the diagnosis only among patients with both 1) unexplained severe pneumonia and 2) epidemiologic evidence that could suggest SARS, including a link to a cluster of cases of unexplained pneumonia, a history of recent travel (or close contact to an ill traveler) to a previously SARS-affected area, or employment as a healthcare worker with direct patient care responsibilities (Table 2). For persons who are healthcare workers or who have traveled to previously SARS-affected areas, evidence of clustered pneumonia cases would further increase the index of suspicion. In addition, atypical pneumonia in a person who works in a laboratory that contains live SARS-CoV should raise the possibility of SARS.

In the absence of pneumonia, history of travel to a previously SARS-affected area is likely to have an extremely low positive predictive value for detecting SARS among patients with respiratory illness and, if used as a screening tool, would likely result in an unacceptable burden on the public health system. (U.S. travelers alone make almost 5 million trips to Asia every year, and respiratory symptoms are common among returning travelers [41,42].)

Clinicians practicing within previously SARS-affected areas may have to adopt a different approach to detecting SARS among patients with pneumonia, such as requiring both evidence of clustering and a typical combination of laboratory and radiologic findings. Clinical algorithms that use more stringent criteria are being developed and will require further validation (31,43).

Evaluating Patients after Documentation of SARS Anywhere in the World

Once SARS activity has been documented anywhere in the world, the positive predictive value of even early clinical symptoms, while still low (21), is more acceptable if used in combination with an epidemiologic link to settings in which SARS has been documented. Therefore, in addition to evaluating all patients with unexplained pneumonia as described above, all patients with fever or respiratory symptoms should be screened for a history of exposure to persons with SARS, travel to areas where SARS transmission is suspected, or contact with ill persons with such a travel history.

In a community where transmission of SARS-CoV is widespread and many cases have no identifiable link to well-defined epidemiologic settings, a provisional diagnosis should be considered for any patient with fever or respiratory illness. The relationship between the clinical history, exposure history, and level of SARS activity in the surrounding community are summarized in Table 2.

The diagnosis of nosocomial SARS among patients hospitalized in either acute or long-term-care facilities may be particularly challenging, since many inpatients may have other reasons for having fever, respiratory symptoms, or pneumonia, and persons with other underlying illnesses may not have typical symptoms. Unrecognized nosocomial SARS was an important factor in spread of disease in the recent outbreaks described in Toronto, Singapore, and Taiwan (12,13,44). Therefore, clinicians and public health professionals must stay particularly vigilant about evaluating fever and respiratory illnesses among inpatients if there have been recent SARS infections in the same facility (44).

Management Decisions after Provisional Diagnosis

If a provisional diagnosis of SARS is made on the basis of the clinical and epidemiologic factors discussed, the patient should be managed according to existing guidance for SARS isolation precautions while evaluation and treatment proceed (45). The clinical evaluation should include, in addition to testing for SARS-CoV, laboratory testing for alternative diagnoses that could explain the illness. The

-acquired

[a]

	Clinical features	Epidemiologic features
	Patients with severe pneumonia of unknown cause	Recent exposure to other persons with unexplained pneumonia
		Recent travel to previously SARS-affected area or close contact with ill persons with a history of travel to such areas[b]
		Healthcare worker[c]
documented	All patients with fever, especially accompanied by headache, myalgias, rigor	Close contact with a person with known or suspected SARS
	Any patient with lower respiratory tract symptoms	Exposure to any place in which active transmission of SARS is documented or suspected
	Patients with severe pneumonia of unknown cause	Close contact with a person with known or suspected SARS
		Exposure to any place in which active transmission of SARS is documented or suspected
		If none of the above: Recent exposure to other persons with unexplained pneumonia Recent travel to previously SARS-affected area or close contact with ill persons with a history of travel to such areas Healthcare worker

The possibility of severe acute respiratory syndrome (SARS) should be considered for any patient with both the clinical and epidemiologic features described, depending -associated coronavirus infection should be

rs, or exposure to persons with pneumonia while traveling in a previously SARS-affected area.

Previously SARS-affected areas include areas in Southeast Asia in which SARS may originate and neighboring areas that may be at risk for early spread because of

Healthcare worker defined as one who has direct patient-care responsibilities. In addition, atypical pneumonia in a person who works in a laboratory that contains live -CoV should raise the possibility of SARS.

patients should be isolated for the duration of the period of communicability or until convincing evidence against SARS is documented. Although the duration of communicability is not known, in the recent outbreak the isolation of patients until 10 days after their fever was gone and their respiratory symptoms were improving seemed an effective method to prevent additional transmission (45,46).

Alternative Diagnoses

Documenting the presence of other diseases does not exclude the possibility of SARS because patients with SARS-CoV infection can be co-infected with other respiratory pathogens (19,47). If the presence of an alternative diagnosis is to be used as justification for discontinuing SARS-specific isolation precautions, the alternative diagnoses should be based only upon tests with high positive predictive value, and the clinical illness should be fully explainable by the diagnosis. The possibility of secondary infection should be considered if the diagnosis of bacterial pneumonia is confirmed, since bacterial pneumonia is a well-known complication of viral respiratory tract infection and may occur following SARS-CoV infection.

Particular care should be taken in completely attributing the illness to an alternative diagnosis if the epidemiologic link to others known to have SARS-CoV infection is strong, or if the patient is part of an epidemiologic cluster of similar illnesses. In the latter instance, confirming an alternative diagnosis among more than one person within the cluster may be used as evidence against SARS, particularly if the clinical findings are not typical of SARS (e.g., upper respiratory symptoms).

Ruling out SARS

The only currently available laboratory method for excluding the diagnosis of SARS-CoV infection is to obtain a negative result on serologic testing of a convalescent-phase serum sample obtained >28 days after onset of symptoms. For patients without evidence of pneumonia at the initial evaluation, serial observations over time may be helpful in identifying those in whom isolation precautions can be safely discontinued (21). Resolution of symptoms and lack of development of radiographic evidence of pneumonia by the 2nd week of illness argue against the diagnosis of SARS. Some patients with mild illness may be missed when this approach is used, but if that is the case, they likely will not play an epidemiologically important role in transmission.

Patients with documented pneumonia who have been given the provisional diagnosis of SARS should be treated as if they have SARS-CoV infection, unless there is convincing evidence for an alternative diagnosis or new epidemiologic information excludes the possibility that the patient was exposed to SARS

Importance of Communication

Because early recognition of SARS depends upon identifying the epidemiologic linkage to SARS-affected persons or places, clinicians must remain updated with current information regarding the locations of SARS activity in

order to obtain the appropriate history from the patients with fever or respiratory illness. Mechanisms for rapid communication between clinicians and public health agencies must be in place so that physicians can be updated frequently as outbreaks evolve both locally and globally. Such lines of communication will also be important in helping public health agencies more rapidly identify emerging areas of activity (such as clusters of illness) through clinician reports of patients with risk factors for SARS.

Similarly, communication among health authorities in different jurisdictions in a region and among countries around the world will be essential to assess risk for exposure for travelers returning from those areas. Information on SARS can be obtained from CDC and WHO Web sites, among others (available from: URL: http://www.cdc.gov and URL: http://www.who.int).

Conclusions

The framework that we have discussed for the early recognition of patients with SARS is based upon the knowledge and experience gathered during the recent worldwide outbreak, which suggests that clinical features alone cannot be used to conclusively distinguish SARS from other respiratory illnesses rapidly enough to inform early management decisions in a practical manner. Clinical features must be interpreted in the context of key epidemiologic risk factors, including epidemiologic linkage to other persons with pneumonia (i.e., clusters of cases of pneumonia clinically compatible with SARS), exposure to settings in which SARS activity is suspected or documented, and pneumonia among healthcare workers with direct patient care. Surveillance and additional research will be critical to help refine the epidemiologic, clinical, and laboratory features used to identify future infections with SARS, which will in turn help with the early detection and prevention of transmission of SARS-CoV infections.

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Clinical Description of a Completed Outbreak of SARS in Vietnam, February–May 2003

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We investigated the clinical manifestations and course of all probable severe acute respiratory syndrome (SARS) patients in the Vietnam outbreak. Probable SARS cases were defined by using the revised World Health Organization criteria. We systematically reviewed medical records and undertook descriptive statistical analyses. All 62 patients were hospitalized. On admission, the most prominent symptoms were malaise (82.3%) and fever (79.0%). Cough, chest pain, and shortness of breath were present in approximately one quarter of the patients; 79.0% had lymphopenia; 40.3% had thrombocytopenia; 19.4% had leukopenia; and 75.8% showed changes on chest radiograph. Fever developed on the first day of illness onset, and both respiratory symptoms and radiographic changes occurred on day 4. On average, maximal radiographic changes were observed on day 10, and fevers subsided by day 13. Symptoms on admission were nonspecific, although fever, malaise, and lymphopenia were common. The complications of SARS included invasive intubation and ventilation (11.3%) and death (9.7%).

The global outbreak of severe acute respiratory syndrome (SARS) has been epidemiologically linked to an outbreak that is believed to have begun during November 2002 in Guangdong Province, People's Republic of China (1). SARS then spread to other countries and regions, such as the Hong Kong Special Administrative Region of China, Vietnam, Singapore, Canada, and Taiwan. By the end of the outbreak, 26 countries had reported 8,098 probable cases of SARS and 774 deaths (2).

Coronavirus was first hypothesized to be the etiologic agent of SARS by Peiris et al. (3). Later, two independent teams (4,5) confirmed the novel coronavirus was associated with SARS infections in patients from Hong Kong, Vietnam, Canada, and Taiwan. This article describes the clinical and laboratory features of patients with SARS in Hanoi, Vietnam.

Methods

Case Definition and Ascertainment

We used the World Health Organization (WHO) case definition (April 1 revision) for SARS in this investigation (6). A probable case-patient was defined as a person who sought treatment after November 1, 2002, with a high fever (>38°C) and cough or breathing difficulty and infiltrates shown on chest radiograph consistent with pneumonia or respiratory distress syndrome. A probable case-patient was excluded if an alternative reason could fully explain the illness, e.g., proven tuberculosis or clinical response within 48 hours to antibacterial therapy. For practical purposes, we modified the case definition to only include cases occurring on or after February 23, the date of onset of symptoms of the Vietnam index case. Serologic testing for SARS-associated coronavirus (SARS-CoV) was performed on serum specimens as previously described (4).

Case-patients were identified by clinicians, and considerable effort was made by the Vietnam Ministry of Health to train both metropolitan and rural staff in surveillance and identification of SARS. Many case-patients were admitted to hospital with suspected SARS; however, only

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those whose condition conformed to the WHO case definition are included in this analysis.

The medical records of SARS case-patients were retrospectively reviewed by physicians. We used a standardized data collection form to record patient information. For the nine patients admitted to the hospital after March 20, clinical data were collected prospectively. For each case-patient, clinical signs, symptoms, radiologic findings, and data from biochemical, hematologic, and microbiologic tests throughout the course of illness were recorded. When assessing the proportion of case-patients with symptoms, if the information about a symptom was not recorded, we assumed the symptom did not occur. For the hematologic and biochemical course of illness, all available measurements were used, with recordings for ≥15 case-patients per day, and the measurements are displayed with accompanying standard deviation of means. Onset of illness was defined as the date when each case-patient first reported feeling unwell with symptoms compatible with SARS.

Data Analysis

Data from the medical records were entered into Microsoft Excel and analyzed with Epi-Info version 6 software. We analyzed the data by using standard descriptive statistical techniques. To describe the course of the illness, the maximum temperature, leukocyte count, platelet count and lymphocyte count data from every case were combined and averaged for each day of the illness.

Results

The first SARS case-patient in Vietnam was admitted to the hospital on February 26, 2003, and the last case-patient was admitted on April 8, 2003. All 62 patients with probable SARS were admitted to hospitals in Hanoi, Vietnam. The initial case-patients were admitted to a small private hospital (hospital A), and the later case-patients were admitted to a facility at a large public hospital, hospital B. Of the 62 case-patients, 61 (98.4%) were seropositive for SARS-CoV. The number of case-patients who were suspected of having SARS but later excluded is not known.

Study Population

The mean age of SARS patients was 40.8 years (median 43, range 20–76 years) and 39 (62.9%) were female. A detailed description of the epidemiology of the SARS outbreak in Vietnam will be published separately.

Clinical Features

Symptoms

The most prominent symptoms on admission were malaise and myalgia (Figure 1). Less than one quarter of the patients had symptoms of the lower respiratory tract on admission; dry cough (22.6%), chest pain (24.2%), and dyspnea (19.4%). The proportion of patients who reported dry cough at any time throughout the illness increased to 90.3%. Other lower respiratory tract symptoms also became more prominent after admission. Upper respiratory tract symptoms were reported infrequently.

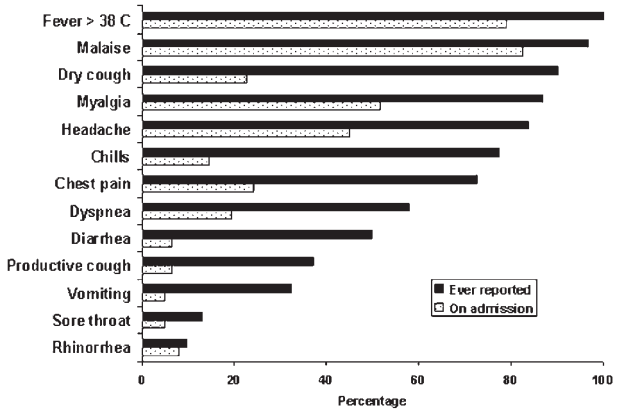

Figure 1. Symptoms of patients with probable severe acute respiratory syndrome (N = 62), at hospital admission and reported during the course of illness, Vietnam, February–May 2003. Note: All case-patients had fever during their illness because this was part of the case definition.

Signs

Fever was present at admission for 79.0% of case-patients, with 66.1% having fever >38°C, although, as per the case definition, all case-patients experienced fever during their illness. Crepitations were present on admission in 35.5% of patients, and in 87.1%, crepitations developed during the course of their illness. On admission, 47 (75.8%) patients had abnormal chest radiographic results. The radiographs of the remaining 15 case-patients showed abnormalities 2 to 7 days (median 5) from the admission date.

On admission, the radiographic changes were mainly interstitial infiltrates, bilateral or unilateral, affecting less than two thirds of the lungs. Maximal radiographic changes during the illness were mainly bilateral interstitial infiltrates or bilateral alveolar opacities affecting more than two thirds of both lungs. The degree of change on the chest radiograph did not always appear to correlate with the apparent severity of illness as defined by the need for respiratory support.

The mean white blood cell count on admission was 5.9 x 10^9/L, ranging between 2.7 and 16.3 x 10^9/L (Table). Leukopenia was found in 19.4% of patients, and lymphopenia occurred in 79.3% of case-patients on admission, with lymphopenia defined as total lymphocyte count below 1.5 x 10^9 /L. Thrombocytopenia was observed in 40.3% of patients on admission, with a mean platelet count of 160.7 x 10^9/L.

Table. Hematologic and biochemical features of patients with severe acute respiratory syndrome on admission

Parameter	Range		Mean	Median	Normal range	Abnormal		N
	Low	High				% Low	% High	
Leukocytes (× 10^9/L)	2.7	16.3	5.9	5.3	4–10	19.4	6.5	62
Neutrophils (%)	44.0	92.8	70.7	71.0	40–75	–	37.1	62
Lymphocytes (%)	4.7	50.0	22.4	22.0	20–45	38.7	3.2	62
Lymphocyte count (× 10^9/L)	0.3	2.2	1.1	1.1	>1.5	79.3	–	58
Hemoglobin (g/L)	88	216	132.4	132.0	125–155	25	1.7	60
Hematocrit (%)	27.3	46.8	38.8	38.6	40.0–52.0	25	1.7	60
Platelets (× 10^9/L)	53	293	160.7	158.0	150–450	40.3	–	62
C-reactive protein (mg/L)	1	136	24.7	17.0	0–8	–	75	44
Alanine aminotransferase (UI/L)								
Hospital A	8.0	36.0	22.3	22.0	10–50	3.4	34.5	12
Hospital B	13.0	294.0	70.0	49.0	≤40			17
Aspartate aminotransferase (UI/L)								
Hospital A	23.0	89.0	43.7	38.0	10–50	–	42.9	11
Hospital B	19.0	550.0	101.0	57.0	≤37			17
Sodium (mmol/L)	129	148	137.1	138	135–145	29.6	3.7	27
Potassium (mmol/L)	3.3	4.7	3.9	3.9	3.5–5.0	14.8	–	27
Creatinine (mg/L)	48	133	93.2	93.0	5.6–12.4	4.5	9.1	22

Twenty-seven of the patients had biochemical blood tests performed. For these patients, 34.5% had elevated alanine aminotransferase levels, and 42.9% had abnormally high levels of aspartate aminotransferase. We observed hyponatremia in 29.6% of patients on admission, and 14.8% of patients had hypokalemia.

Natural History of Illness

The average maximum temperature for all of the case-patients on day 1 of onset was 38.7°C and reached a maximum of 39.0°C on day 5 (Figure 2). We observed that fever in SARS patients subsided on day 13. Overall, the average leukocyte count of all the cases never decreased below 4.0 × 10^9/L, suggesting that leukopenia was not a common feature of SARS among the whole cohort, but did occur in a few patients, as indicated by the error bars on Figure 2. Thrombocytopenia (platelet count < 150 × 10^9/L) was present in the cohort from day 4 until day 9 of the illness. After day 10, the average platelet count returned to within the normal range. Lymphopenia (lymphocyte count <1.5 × 10^9/L) was present throughout the course of the illness, with lymphocyte counts ranging from 1.0 to 1.5 × 10^9/L.

The natural history of SARS in Vietnam is shown in Figure 3. Not all patients felt feverish at onset, but fever developed an average of 0.3 days after the onset of other SARS symptoms. We observed that the average length of time from onset to observed radiographic changes and from onset to first respiratory symptoms were similar (4.4–4.8 days) and generally coincided with admission to hospital. Maximal radiographic changes occurred on the 10th day of illness, on average, 3 days before fever subsided. SARS patients were in hospital for, on average, 24.5 days (± 7.4 days). A total of six (9.7%) case-patients died. We observed that the time from symptom onset to admission decreased during the outbreak (data not shown).

Case Management

Respiratory Therapy

Respiratory assistance was required for 38 (61.2%) of the patients: 25 (40.3%) patients required the use of supplemental oxygen; 6 (9.7%) required positive pressure noninvasive ventilation while an additional 7 (11.3%) patients were intubated and received mechanical ventilation. Only 1 of the 7 who were intubated recovered.

Antibiotics

A wide range of antibiotics were prescribed for SARS patients in Vietnam, including beta-lactams, tetracyclines, aminoglycosides, macrolides, and fluoroquinolones. Antibiotic therapy was not observed to be clinically beneficial.

Antivirals

Patients in the first wave of the outbreak of SARS were initially treated with oseltamivir when the etiologic agent was thought to be an influenza virus. Eighteen patients (29.0%) received oral or intravenous ribavirin for an average of 9 days (median 12 days) after the onset of illness. Neither oseltamivir nor ribavirin was observed to have any clinically beneficial effect on the course of illness.

Steroids

For 14 patients, steroid treatment was begun an average of 8.2 days after the onset of illness (median 7 days). Patients were given steroids for a mean duration of 7.6 days (range 1–14 days). No particular protocol existed for

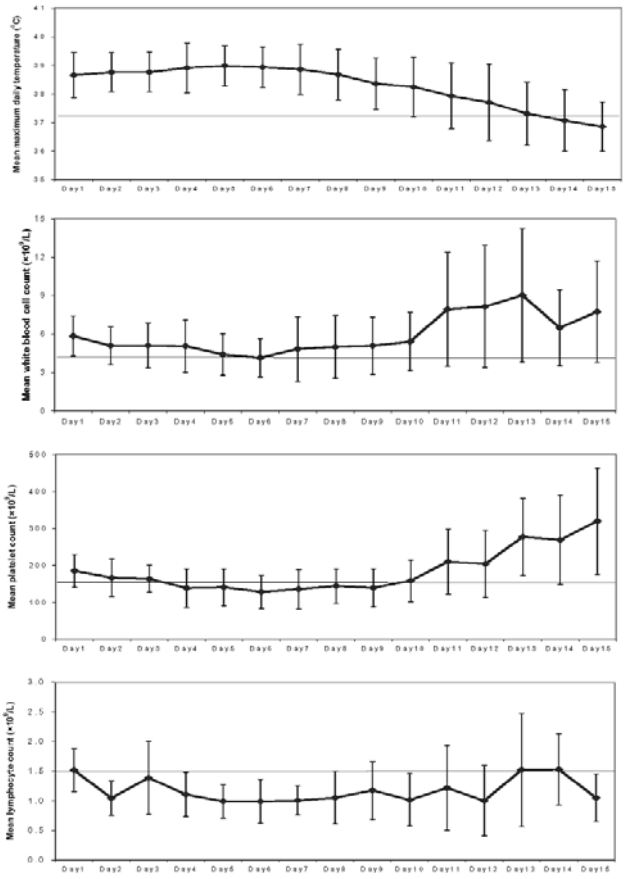

Figure 2. Average (±1 standard deviation) maximal daily temperature, leukocyte count, platelet count, and lymphocyte count by day of severe acute respiratory syndrome from onset, Vietnam, February–May 2003, (N = 62 cases but not for each data point).

the timing or dosage of steroids given, making interpretation of effectiveness difficult.

Discussion

This is the first report of a complete outbreak of SARS and as such includes all patients in whom SARS was diagnosed from the beginning of the outbreak until SARS was declared contained in Vietnam on April 28, 2003. Dr Carlo Urbani (deceased), a public health physician with WHO in Vietnam, first described the outbreak in reports to WHO at the beginning of March 2003. He reported a similar presentation of case-patients that we describe. The main clinical features of probable SARS case-patients reported in Vietnam were fever, malaise, dry cough, and infiltrates on radiographs. These findings are consistent with those reported in Hong Kong (3,7), Singapore (8), and Canada. (9) Additionally, we have described the clinical development of SARS over time. The main feature exhibited by SARS case-patients on hospital admission was fever, which typically lasted 13–14 days after onset.

Lymphopenia was constant throughout the illness and thrombocytopenia, on average, lasted for 5 days, beginning on the fourth day after onset. Respiratory symptoms and the first radiographic changes were first noted on day 4 of the illness. Maximal radiograph change generally occurred on day 10.

On admission, 6.5% of patients reported having diarrhea. However, patients with SARS may have recalled respiratory symptoms more frequently than gastrointestinal symptoms. During the full course of illness, half of the probable SARS case-patients reported diarrhea. What proportion of these patients had diarrhea directly related to SARS or in response to antibiotic treatment is not known. Diarrhea, regardless of its cause, has important implications for transmission of SARS, because SARS-CoV can be shed in feces (10). However, it is not yet known whether viable organisms are shed in quantities sufficient to constitute a substantial source for transmission. The role of diarrhea in SARS transmission requires further investigation.

Our data on clinical symptoms at admission may not be generalizeable to other SARS outbreaks for several reasons. Admission bias may have occurred at hospital A after the initial cluster among healthcare workers was recognized. In some instances, temperatures were being taken and some patients were admitted after fever onset but no other symptoms, daily chest x-rays were taken for some case-patients, and some patients refused admission until after they had been ill for several days.

Microbiologic evaluation of patients who met the case definition for probable SARS in Vietnam was difficult at the time of admission. Decisions about case status on admission were initially made by considering clinical signs and symptoms. We did not have laboratory facilities to confirm SARS, and facilities to identify other agents causing atypical pneumonia were limited. Patients were treated with antibiotics for atypical bacterial pneumonia on admis-

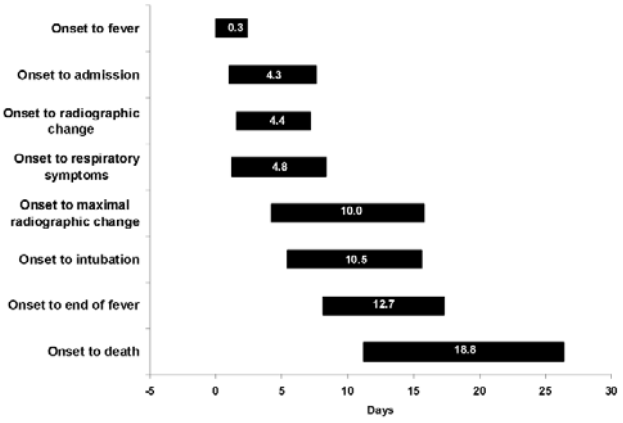

Figure 3. Average (±1 standard deviation) duration of time from onset of illness until outcome in the evolution of severe acute respiratory syndrome, Vietnam, February–May 2003

sion to hospital, and if the patients responded to treatment within 48 hours, the SARS case status was revised.

All case-patients with probable SARS in the Vietnam outbreak were epidemiologically linked, and 98.4% had serologic evidence of SARS-CoV infection. After the initial case, all probable SARS cases identified in the Vietnam outbreak were among healthcare workers or close contacts of case-patients.

Our findings in regard to treatment are nonspecific. Proven treatment options must await proper clinical trials in other centers.

Despite the nonspecific nature of SARS at clinical presentation, a typical case had fever, myalgia, malaise followed several days later by cough and respiratory symptoms. At this point the patient typically had changes shown by chest x-ray, lymphopenia, and thrombocytopenia. Due to the nonspecific nature of SARS, both on admission and throughout the course of illness, clinicians must obtain a detailed exposure history for anyone presenting with atypical pneumonia to help in the early diagnosis and management of a potential outbreak situation. When the diagnosis is in doubt, the person should be isolated under strict infection control procedures until the diagnosis becomes clear.

Acknowledgments

We dedicate this paper to the late Dr. Carlo Urbani, who provided the first epidemiologic and clinical descriptions of SARS and died from SARS as a result of his early investigation.

We thank the Ministry of Health, Vietnam, for support of our efforts, especially Minister of Health Tran Thi Trung Chien, Vice Minister of Health and Chair of the SARS Taskforce Nguyen Van Thuong, Le Thi Thu Ha, and the many persons in the Ministry of Health who assisted us. We also thank Pascale Brudon, Rodger Doran, Helen-Louise Taylor, the WHO staff in Vietnam, and other members of the WHO SARS team in Vietnam, Manila, and Geneva; Nguyen Ngoc Tho and J. Gouzee, who provided clinical care to the patients; and the staff of the Ha Noi French Hospital and the Tropical Medicine Institute at Bach Mai Hospital. Lastly, we acknowledge the patients with SARS and their families.

Dr. Vu is a clinical immunoallergist and was the primary clinician looking after the SARS patients at hospital A. Since the outbreak of SARS, Dr. Vu has been involved in a range of research projects concerning SARS.

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Index Patient and SARS Outbreak in Hong Kong

Raymond S.M. Wong* and David S. Hui*

During the global outbreak of severe acute respiratory syndrome (SARS) in 2003, treatment was empiric. We report the case history of the index patient in a hospital outbreak of SARS in Hong Kong. The patient recovered after conventional antimicrobial therapy. Further studies are needed to address treatment of SARS, which has high attack and death rates.

Severe acute respiratory syndrome (SARS), a new disease that is highly contagious, has caused a major impact worldwide. Treatment of this disease remains empiric. This report describes the natural history of a case of SARS in a young, previously healthy patient who received no specific therapy for infection with SARS-associated coronavirus (SARS-CoV). He was the index patient in a large hospital outbreak in Prince of Wales Hospital in Hong Kong (1).

Case Report

In early March 2003, a 26-year-old man was admitted to a general medical ward of the Prince of Wales Hospital; he had been ill for 1 week with fever, chills, and rigor. He had had a cough productive of whitish sputum for 2 weeks. He also had diarrhea and had vomited several times before his admission. His previous health had been good, and he had no history of recent travel. Physical examination showed a temperature of 40.2°C and bronchial breath sounds at the right upper zone lung field. Chest x-ray confirmed right upper lobe consolidation (Figure, part A).

A complete blood profile on admission showed a leukocyte count 3.1 x 10^9/L, absolute neutrophil count 2.0 x 10^9/L, lymphocyte count 0.7 x 10^9/L, platelet count 112 x 10^9/L, and hemoglobin 14.7 g/dL. The patient had mild renal impairment, with a creatinine of 119 μmol/L, urea and electrolytes within normal limits, and alanine transaminase mildly elevated at 90 IU/L (normal <58 IU/L). Bilirubin, alkaline phosphatase, and albumin levels were normal. C-reactive protein was 6.5 mg/L (normal <9.9 mg/L). A diagnosis of atypical or viral pneumonia was suspected because of the low leukocyte count and normal C-reactive protein. Other laboratory tests were performed, including blood, sputum, and urine cultures, nasopharyngeal aspirate for influenza and parainfluenza, indirect immunofluorescence for respiratory syncytial viral antigen detection, and atypical pneumonia titer (for adenovirus, *Chlamydia psittaci*, Q fever, influenza A and B, and *Mycoplasma*). The patient received treatment with intravenous amoxicillin-clavulanate and oral clarithromycin.

The patient was housed in a general medical ward with no specific isolation facility. After admission his high fever and productive cough, now with thick, yellowish sputum, persisted. He also complained of progressive dyspnea, headache, dizziness, generalized malaise, and myalgia. His pulse and blood pressure were normal, and his oxygen saturation was approximately 98% on room air. A sputum culture yielded normal oral flora, and sputum smears were negative for acid-fast bacilli. Nasopharyngeal aspiration was negative for influenza viruses A and B, respiratory syncytial virus, adenovirus, and parainfluenzavirus types 1, 2, and 3, with the use of commercial immunofluorescence assay. A chest radiograph on day 4 showed progression of pneumonia, with consolidation changes over the right upper and lower lobes (Figure, part B). A repeat complete blood profile showed a leukocyte count of 5.4 x 10^9/L with persistent lymphopenia and a platelet count of 98 x 10^9/L. Amoxicillin-clavulanate was therefore changed to intravenous cefotaxime, 1 g every 8 h; clarithromycin (500 mg twice a day) was continued. As the patient's condition deteriorated progressively and he had difficulty in expectorating sputum, salbutamol, 0.5 g four times a day, driven by a jet nebulizer at 6 L of oxygen per min, was given to assist mucociliary clearance. His oxygen saturation remained normal without supplemental oxygen.

Starting from day 6, the patient's fever and chest condition gradually improved. However, over the next 2 weeks, 138 persons (mostly healthcare workers) who had been in contact with him had onset of a similar illness with high fever and pneumonia. The patient was subsequently con-

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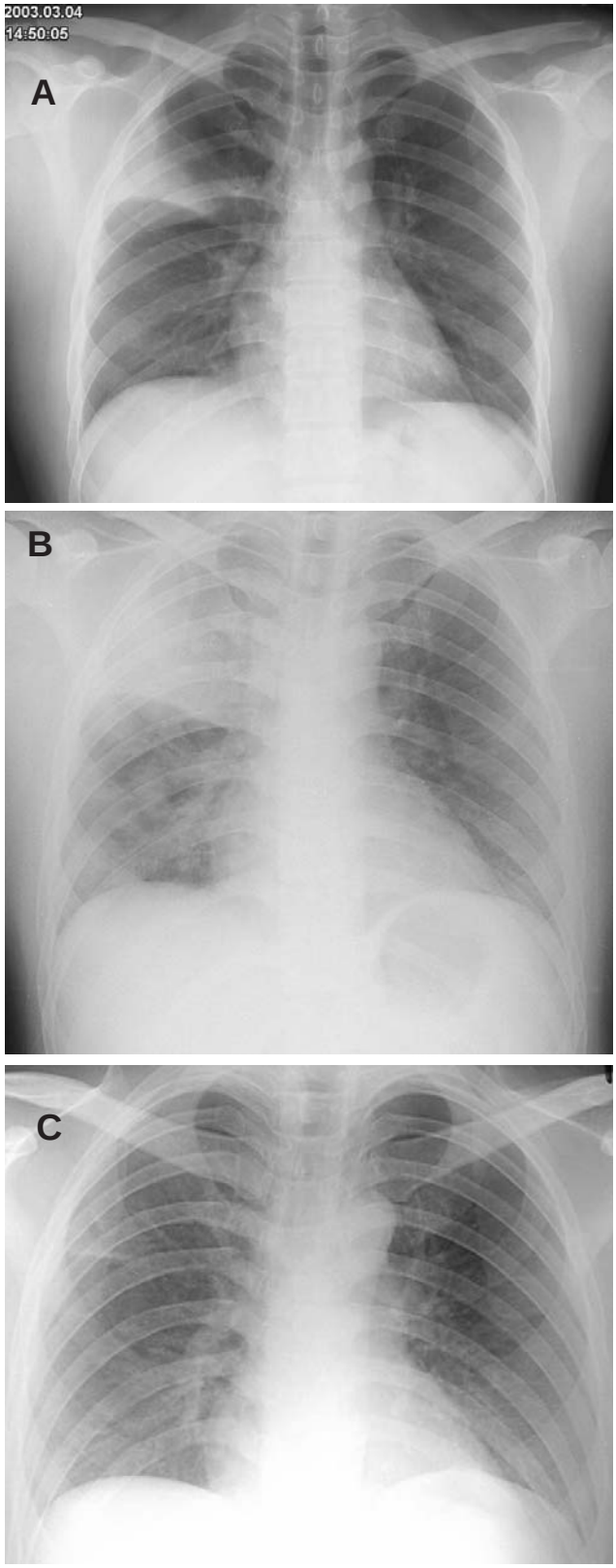

Figure. Chest radiographs performed A, at admission, B, on day 4, and C, on day 16 of hospitalization for index SARS case-patient, Prince of Wales Hospital.

firmed to be the index case-patient in this hospital outbreak of SARS (1). Three family members were also infected. Further history showed that he had visited a hotel in Kowloon, Hong Kong, where a 64-year-old physician from southern China had stayed for 2 days; this physician later died of severe atypical pneumonia 10 days after admission to a regional hospital in Kowloon (2). The cause of the illness was not known at the time of the physician's death.

Our patient was identified as the index case-patient 5 days after the onset of this large outbreak at the Prince of Wales Hospital, as he was the first patient who had the characteristic clinical, radiologic, and laboratory features of SARS and had epidemiologic links with other infected persons. After 8 days, use of the nebulized bronchodilator was stopped because of the possibility of enhancing SARS transmission, and the patient was isolated in a private room with negative-pressure ventilation. Healthcare workers entering the room wore disposable gloves and N95 masks. After the patient completed a 7-day course of cefotaxime and a 10-day course of clarithromycin, his pneumonia recovered gradually, and serial chest radiographs confirmed resolution of his consolidation (Figure, part C). His diarrhea and other systemic symptoms also resolved spontaneously.

An immunofluorescence test for antibody against SARS-CoV subsequently confirmed an elevated titer of 1:5,120 in convalescent-phase serum collected on day 21 of illness. Polymerase chain reaction of nasopharyngeal aspirate was negative for coronavirus. Convalescent-phase serum was negative for other atypical pneumonia organisms, including adenovirus, *C. psittaci*, Q fever, influenza A and B, and *Mycoplasma*. Repeat complete blood count showed that lymphocytes and thrombocytes had returned to normal, along with serum creatinine and alanine transaminase levels.

The patient was isolated in a private room until day 27 of his hospital stay, when his nasopharyngeal aspirate and urine samples were confirmed to be negative for SARS-CoV. Repeat chest radiograph at follow-up 2 weeks later showed no residual parenchymal opacity, and the patient remained asymptomatic.

Conclusions

This report describes the index patient responsible for the hospital outbreak in the Prince of Wales Hospital (2). He was linked to spread of the virus to more than 100 persons (1). This outbreak, together with similar events in Canada (3), Singapore (4) and other cities where the source of infection was also related to the Chinese physician (5), led to increased awareness of this emerging global infection caused by a novel coronavirus (6). The superspread event in Prince of Wales Hospital caused by this

patient was related to failure to apply isolation precautions, as the disease had not been recognized during the early part of his admission. The use of a nebulized bronchodilator may also have enhanced the spread of the virus in the ward, and this practice was stopped for patients with suspected SARS after this incident (7).

This case report illustrates the natural history of SARS in a young, previously healthy patient who received no specific therapy. His clinical features and laboratory parameters were similar to those of other patients with SARS (2–5). His clinical course followed a typical pattern with progression of pneumonia during the 2nd week of his illness (8). He was treated presumptively for bacterial community-acquired pneumonia with conventional antimicrobials (9), without antiviral agents or corticosteroids. He started to improve by the 3rd week and subsequently recovered uneventfully.

During the global outbreak in 2003, treatment of SARS was empiric. Several groups have reported the use of ribavirin (2–5,7,8) and corticosteroids (2,3,7,8,10,11) with generally favorable outcomes. Ribavirin has been associated with substantial adverse reactions, including hemolytic anemia, elevated transaminases, and bradycardia (4), and has demonstrated no in vitro activity against SARS-CoV (12). Further studies, preferably with a randomized, placebo-control design, are needed to address treatment of this disease, which has high attack rates and is frequently fatal.

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Possible Central Nervous System Infection by SARS Coronavirus

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On day 22 of illness, generalized tonic-clonic convulsion developed in a 32-year-old woman with severe acute respiratory syndrome (SARS). Cerebrospinal fluid tested positive for SARS coronavirus (SARS-CoV) by reverse transcriptase–polymerase chain reaction. SARS-CoV may have caused an infection in the central nervous system in this patient.

Severe acute respiratory syndrome (SARS) is an acute febrile illness predominantly involving the lungs, and a high proportion of patients die of respiratory failure (1). However, the novel coronavirus causing SARS appears not to be confined to the lungs, as suggested by observation of diarrhea (2), impaired liver function tests, lymphopenia, and thrombocytopenia (3). We report a case of possible involvement of the central nervous system by the SARS-coronavirus (SARS-CoV).

Case Report

A 32-year-old woman in week 26 of pregnancy, who was previously in good health, was admitted to the hospital on March 29, 2003 with myalgia for 1 week and fever, chills, and rigor for 2 days. She had an unproductive cough and no sore throat. On admission, her temperature was 38.8°C, with chest radiograph showing patchy consolidations over the right upper lobe and both lower lobes. Total leukocyte count was 12.3×10^9/L and lymphocyte count was 1.6×10^9/L. Hemoglobin level, liver and renal function tests, and serum lactate dehydrogenase were normal. Ribavirin (500 mg every 8 hours) and hydrocortisone (100 mg every 8 hours) were administered intravenously. Clinical and radiologic deterioration progressed, and by day 7, mechanical ventilation was begun. Onset of acute renal failure began on day 8, with oliguria and rapidly elevating serum urea and creatinine levels, and a decision was made to terminate the pregnancy. Lower-segment cesarean section was performed on the same day, and a baby girl, appropriate to the gestational age, was born. Mechanical ventilation continued, but renal function continued to deteriorate. She was given piperacillin/tazobactam to cover possible sepsis. On day 10, the serum creatinine level was 504 μmol/L, and the patient was still oliguric, necessitating hemodialysis intermittently from day 10 to day 18. The diuretic phase occurred on day 19, and her renal functions improved progressively.

On day 22, the patient was still on mechanical ventilation and was sedated with an infusion of 30 mg of midazolam plus 30 mg of morphine in 50 mL 5% dextrose solution at 6 mL per hour. During the previous 2 days, she had a low-grade fever. Early that afternoon she had a generalized tonic-clonic convulsion with loss of consciousness and up-rolling eyeballs lasting for 1 minute. She had no neck rigidity and no residual neurologic deficit. Lumbar puncture performed later that day showed an opening pressure of 15 cm of water, with free flow of clear cerebrospinal fluid (CSF). Total CSF protein was 0.38 g/L, and CSF glucose was 5.1 mmol/L, against blood glucose of 6.6 mmol/L. Microscopy showed an erythrocyte count of 20 per mm^3 and a leukocyte count of <1 per mm^3. Gram stain, bacterial cultures, and viral cultures were negative. However, reverse transcriptase–polymerase chain reaction (RT-PCR) on CSF for the SARS-CoV was positive. Serum calcium was 1.96 mmol/L against a serum albumin of 27 g/L, serum magnesium was 0.62 mmol/L (normal range 0.7–1.1 mmol/L), serum sodium was 152 mmol/L (normal range 135–149 mmol/L), serum potassium was 4.0 mmol/L, and serum creatinine was 311 μmol/L. Both the electroencephalogram done on day 39 and magnetic resonance imaging done on day 46 showed no abnormalities. She had no other convulsions.

Renal function and respiratory status continued to improve. She was extubated on day 27 and made an uneventful recovery. Immunoglobulin G antibody titer of the SARS-CoV by immunofluorescence assay was <1:25

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on day 1 and 1:1,600 on day 39. In addition to CSF, RT-PCR for SARS-CoV was also positive in stool specimens and peritoneal fluid.

Conclusions

In our patient, the occurrence of generalized convulsion with a positive RT-PCR for SARS-CoV in the CSF suggests possible infection of the central nervous system by SARS-CoV. Other possible causes of convulsion were considered. The slightly high serum sodium that gradually developed over 3 days was likely related to piperacillin/tazobactam administration and was unlikely to be responsible for the convulsion. Cerebral hypoxemia was unlikely, as the patient was monitored closely in the intensive care unit, and records did not show sustained arterial oxygen desaturation. Acute renal failure was also unlikely as the patient's renal function was improving, and one would expect convulsion caused by acute renal failure to occur during the worsening phase or at the height of the renal impairment. Acid-base disturbances were absent. Although serum magnesium was somewhat low (0.69 mmol/L after correction for serum protein concentration using the formula suggested by Kroll and Elin [4]), convulsions are usually associated with much lower levels (5). No hypertension or proteinuria existed to suggest eclampsia. Also, preeclampsia occurs when the placenta is present, and termination of pregnancy is the standard treatment for severe preeclampsia (6). Ribavirin has not been reported to cause convulsion, and it would be very unlikely for such an event to occur 5 days after discontinuation.

The possibility of a false-positive RT-PCR test result was also considered. To our knowledge, a genuine false-positive test has not been reported in the literature in any clinical specimen. Nonetheless, the CSF sample could have been contaminated with the patient's own blood, which contained genetic material of SARS-CoV. However, finding only 20 erythrocytes per mm^3 in the CSF makes this unlikely.

Human coronavirus (HCoV) is responsible for up to one third of upper respiratory tract infections (7). It can enter susceptible cells through the endocytic pathway (8). Two strains (229E and OC43) have been implicated in multiple sclerosis (9,10), and both can persistently infect human oligodendrocytic and neuroglial cell lines (11). More recently, a combination of RT-PCR and Southern hybridization on human brain autopsy samples provided more definitive experimental evidence for the neurotropism and neuroinvasion of HCoV and its possible association with multiple sclerosis (12). Preliminary work in Hong Kong with RT-PCR on SARS autopsy specimens of brain tissue were positive for SARS-CoV, although electron microscopy did not show ultrastructural features of the virus (W.-C. Yu, unpub. data). The findings from our patient are not compatible with multiple sclerosis, and the PCR result suggests that the central nervous system (CNS) is affected by SARS-CoV.

Another lumbar puncture cannot be repeated to test the CSF by RT-PCR. The presence of SARS-CoV in the CNS cannot be firmly established. The possibility also remains that infection of the CNS never occurred, as suggested by the lack of focal neurologic deficit, normal CSF pressure, cell count, and biochemistry. The normal electroencephalogram and magnetic resonance imaging might have missed the pathologic changes, as they were done 17 and 24 days after the event. In the absence of a good alternative explanation for the convulsion, the diagnosis of infection of the CNS by SARS-CoV is still possible, despite a lack of supportive evidence. The hospital has managed a total of 577 definite SARS patients in this period, and this is the only patient who had a convulsion. This was the only single patient who had a lumbar puncture, suggesting that the involvement of the CNS in SARS is rare.

Besides involvement of the lungs and possibly the CNS, no good alternative explanation exists for acute renal failure in this patient. Renal failure could possibly be caused by SARS-CoV involving the kidneys. Additionally, our patient had diarrhea from day 3 to day 20, with positive RT-PCR for SARS-CoV in stool specimens, suggesting involvement of the gastrointestinal tract as well. In conclusion, our case demonstrates that SARS-CoV can possibly infect multiple organ systems and that CNS can potentially be involved.

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SARS and Pregnancy: A Case Report

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We report a laboratory-confirmed case of severe acute respiratory syndrome (SARS) in a pregnant woman. Although the patient had respiratory failure, a healthy infant was subsequently delivered, and the mother is now well. There was no evidence of viral shedding at delivery. Antibodies to SARS virus were detected in cord blood and breast milk.

Severe acute respiratory syndrome (SARS) is a potentially life-threatening, atypical pneumonia that results from infection with a novel virus, SARS-associated coronavirus (SARS-CoV) (1–3). Limited studies and case reports suggest that other viral illnesses during pregnancy are sometimes associated with an increased risk for maternal illness and death (e.g., influenza) (4) and congenital anomalies (rubella and varicella) (5,6). No data exist regarding the effects of previously identified human coronaviruses on pregnancy. However, porcine reproductive and respiratory syndrome virus, an animal virus related to coronaviruses, is commonly associated with early fetal demise in pigs (7). In contrast, infection with feline infectious peritonitis virus, an animal coronavirus, results in newborn kittens' becoming immune carriers of the virus (8). Data are limited regarding the effect of SARS-CoV on human pregnancy (9). We report additional details on the clinical course and outcomes of a case of laboratory-confirmed SARS-CoV infection in a pregnant woman (10).

Case Report

A 36-year-old, previously healthy, Asian woman (gravida 2, para 1) at 19 weeks' gestation with a low-lying placenta traveled in late February from the United States to Hong Kong with her husband and child. Before departing from the United States, the patient had been complaining of a mild, intermittent cough without fever for approximately 10 days. The cough, similar to one she had during her previous pregnancy, did not impair her ability to function. While in Hong Kong, between February 19 and March 2, 2003, she stayed at the same hotel and on the same floor as a physician from southern China, who is believed to have been the source of infection for patients who were the index case-patients in subsequent outbreaks of SARS in Hong Kong, Singapore, Hanoi, and Toronto, Canada (11). On February 24, fever, headache, weakness, anorexia, increasing cough, and shortness of breath developed in the patient. The next morning, she sought medical attention and was prescribed chlorpheniramine and acetaminophen. Her symptoms worsened, prompting her to see another physician 2 days later. A fetal ultrasound performed at this time was reportedly normal. Cephalexin was added to her regimen, but her condition did not improve; that night, she noted blood-tinged sputum.

On March 2, the patient returned to the United States where, acutely short of breath, she was hospitalized with pneumonia. Her highest temperature on admission was 102.5°F (39.2°C). Although chest auscultation was normal, chest radiography showed diffuse bilateral lower lobe infiltrates (Figure, part A). Admission arterial blood gas analysis showed pH 7.47, $PaCO_2$ 31 mm Hg, and PaO_2 75 mm Hg on room air. Other pertinent laboratory findings included a leukocyte count of 3,300/mm^3 (normal range 4,500–11,500/mm^3) with a differential of 83% polymorphonuclear cells, 12% lymphocytes, and 5% monocytes; platelets of 103,000/mm^3 (normal range 150,000–450,000/mm^3); and alanine aminotransferase of 42 U/L (normal range 10–40 U/L). She was given supplemental oxygen for hypoxia and intravenous azithromycin and ampicillin to treat typical and atypical respiratory pathogens associated with community-acquired pneumonia. A fetal ultrasound performed on March 3 demonstrated a live intrauterine fetus of approximately 21 weeks gestational age and complete placenta previa. Despite antibiotic therapy, over the next 3 days, the patient became increasingly dyspneic; rales and decreased breath sounds developed, and she had radiographic evidence of progressive pulmonary infiltrates (Figure, part B). During this time, ticarcillin-clavulanate was added to her antimicrobial

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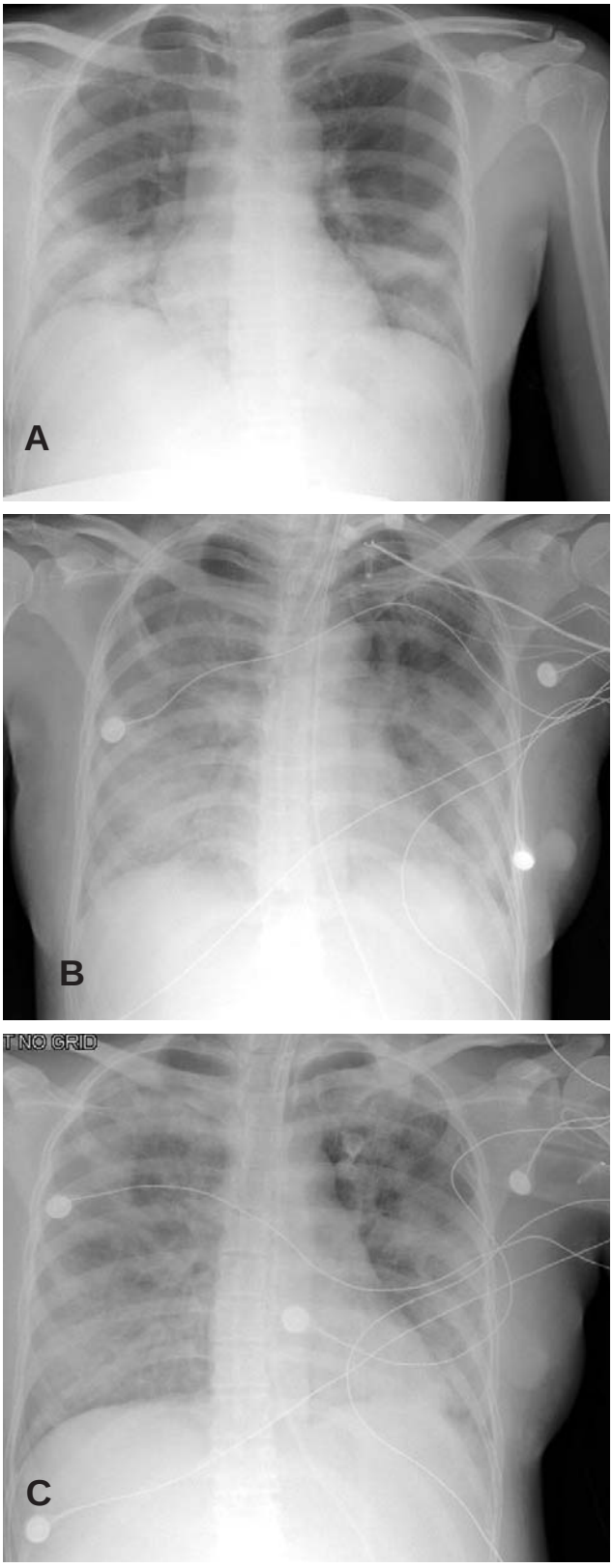

Figure. Chest radiographs of case-patient with severe acute respiratory syndrome (SARS) while pregnant. A, day 6 of illness; B, day 10; C, day 13.

regimen, and rifampin was initiated as adjuvant therapy for possible legionellosis. Because the patient's diagnosis remained elusive, tuberculosis was considered, and she was placed in airborne isolation. Arterial blood gas analysis on March 5 showed: pH 7.48, $PaCO_2$ 31 mm Hg, and PaO_2 57 mm Hg on a 100% nonrebreather mask. The patient was subsequently placed on a mechanical ventilator. When avian (H5N1) influenza was considered in the differential diagnosis, oseltamivir was added to her therapy. During the next several days, she began to improve. Chest auscultation demonstrated few bibasilar rales, and a chest radiograph showed interval improvement (Figure, part C). She was afebrile by March 9 and extubated on March 12. On March 13, she had a fetal ultrasound that showed fetal growth consistent with dates and complete placenta previa. On March 17, she was discharged to home. Sputum, blood, and urine cultures; smears for acid-fast bacilli; and tests for *Legionella* urinary antigen, influenza nasopharyngeal antigen, and cold agglutinins were negative. Serum specimens collected 12 and 29 days after illness onset were tested at the Centers for Disease Control and Prevention (CDC) and found to be positive for SARS-CoV antibody.

A follow-up ultrasound examination on April 29 during routine prenatal care showed fetal growth consistent with dates and persistent complete previa. On May 2 (approximately 30 weeks' gestation), the patient was diagnosed with gestational diabetes after an abnormal oral glucose tolerance test. Her diabetes was well-controlled by diet during the remainder of her pregnancy. Because serial ultrasounds performed on May 28 and June 24 demonstrated complete placenta previa, she underwent a cesarean section at 38 weeks' gestation. A 6-lb, 15-oz (3,145-g) healthy female infant was delivered without complications. Apgar scores at 1 and 5 minutes were 9 and 9. Gross and microscopic inspection of the placenta did not show major abnormalities.

After informed consent was obtained, the following specimens (collected approximately 130 days after illness onset) were submitted to CDC for coronavirus testing: serum, whole blood, nasopharyngeal and rectal swab specimens from the mother, postdelivery placenta, cord blood, amniotic fluid, and breast milk. No viral RNA was detected in specimens tested by reverse transcriptase–polymerase chain reaction. Antibodies to SARS-CoV were detected in maternal serum, cord blood, and breast milk by enzyme immunoassay and indirect immunofluorescence assay (Table).

Conclusions

On the basis of previous reports from Hong Kong, SARS-CoV infection can be associated with critical maternal illness, spontaneous abortion, or maternal death (9,12).

Table. Results of SARS-associated coronavirus (SARS-CoV) testing of specimens from case-patient infected while pregnant[a]

Specimen[b]	SARS-CoV serologic results[c]	SARS-CoV RT-PCR
Maternal serum	+	ND
Maternal whole blood	–	ND
Maternal nasopharyngeal swab	ND	–
Maternal rectal swab	ND	–
Postdelivery placenta[d]	–	–
Amniotic fluid	–	–
Cord blood	+	ND
Breast milk	+	–

[a]SARS, severe acute respiratory syndrome; RT-PCR, reverse transcriptase–polymerase chain reaction; ND, not done.
[b]All specimens listed were collected 127 days after onset of the case-patient's illness with the exception of breast milk, which was collected 131 days after illness onset.
[c]Serologic analysis included enzyme immunoassay and indirect immunofluorescence assay.
[d]Postdelivery placenta also underwent immunohistochemical (IHC) staining; there was no IHC evidence of SARS-CoV.

We have described a serious SARS-associated illness that necessitated mechanical ventilation in a pregnant case-patient. Her pregnancy was also complicated by placenta previa and gestational diabetes—two conditions that she was at increased risk of developing because of advanced maternal age (13). The infant appeared unaffected by the mother's SARS. However, at the time of delivery, clinical specimens from the infant were not available for SARS-CoV testing.

All healthcare workers involved in the delivery and subsequent care of the infant have remained healthy. However, serologic testing for SARS-CoV infection was not performed on these persons. The infant was delivered by cesarean section with contact, droplet, and airborne precautions in place (i.e., staff wore fit-tested N95 respirators and the cesarean section took place in a negative-pressure operating room). Since SARS-CoV was not detected in specimens collected at delivery and the patient delivered months after her illness onset, it is not clear if such precautions were necessary. However, other patients have demonstrated viral shedding in feces (14,15) and peritoneal fluid (16), suggesting that SARS-CoV may be present in other body fluids and hence, transmission during vaginal and cesarean deliveries is plausible. The presence, in this case, of SARS-CoV antibodies in cord blood and breast milk raises the issue of whether SARS-CoV infection during pregnancy results in passive immunity. Serial serologic testing of newborn clinical specimens and breast milk may provide a better understanding of the natural history of the fetal and newborn immune response to SARS-CoV infection during pregnancy.

This report, in conjunction with the reports from Hong Kong (9,12), provides an initial view of the spectrum of illness and outcomes associated with pregnancy-related SARS-CoV infection. A variety of factors might contribute to this range of outcomes (e.g., timing of SARS-CoV exposure during pregnancy; use of steroids, ribavirin, or both; differences in host immune response; the presence of coexisting conditions). More comprehensive epidemiologic and clinical summaries about the course of other SARS-affected pregnancies and long-term follow-up of infants are needed to fully define the pregnancy-related risks of this infection. Data on larger numbers of pregnant women infected with SARS-CoV may help refine infection-control strategies and provide a sound basis for clinical guidelines to manage future cases.

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Atypical SARS and *Escherichia coli* Bacteremia

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We describe a patient with severe acute respiratory syndrome (SARS) whose clinical symptoms were masked by *Escherichia coli* bacteremia. SARS developed in a cluster of healthcare workers who had contact with this patient. SARS was diagnosed when a chest infiltrate developed and when the patient's brother was hospitalized with acute respiratory failure. We highlight problems in atypical cases and offer infection control suggestions.

Severe acute respiratory syndrome (SARS) is a newly recognized condition. In early March 2003, the World Health Organization (WHO) issued case definitions for SARS (1). In most studies, the clinical syndrome includes fever in 100% of patients (2–4). Other common clinical features include chills and rigors (73%), myalgia (60%), and cough (>50%). Some patients initially thought to have SARS have been excluded when tests showed other causes (5). We report a patient whose coexisting conditions masked the diagnosis of SARS, leading to a cluster of suspect and probable cases.

Case Report

A 59-year-old Chinese man was admitted on March 24, 2003, to the Singapore General Hospital. He had previously been hospitalized in Tan Tock Seng Hospital, the hospital in which the first SARS outbreak in Singapore occurred (6), from March 5 to March 20 for diabetic nephropathy.

The patient had multiple coexisting conditions including ischemic heart disease with atrial fibrillation, previous stroke with scar epilepsy, diabetes mellitus with nephropathy (creatinine 242 μmol/L), and peripheral vascular disease. He was not on steroids or traditional medications.

Clinical signs and symptoms were melena and dizziness. He was pale, temperature was 36.5°C, blood pressure was 126/70 mm Hg, and pulse rate was 110/min. Chest examination was normal, and the abdomen was soft. Rectal examination showed melena. The patient also had a sloughy right heel ulcer. Laboratory values are shown in the Table. Antral gastritis was diagnosed on gastroscopy. Colonoscopy and barium enema were unsuccessful because of excessive fecal residue.

The patient had a temperature spike (38.4°C) on March 26, and intravenous (IV) amoxicillin/clavulanic acid was started. His temperature spiked again (38.8°C) on March 28. The source of sepsis was thought to be the necrotic heel ulcer; wound débridement was performed on March 30.

The fever persisted from March 28 until April 2. Blood cultures drawn on March 28 isolated *E. coli* of intermediate sensitivity to amoxicillin/clavulanic acid. Further evaluation for the source of bacteremia included urinalysis, which indicated a leukocyte count of 4 and erythrocyte count of 165. Ultrasonography showed a 2.8-cm abscess at the midpole of the right kidney. Urine culture yielded mixed bacteria growth. The patient's medication was changed to IV ceftriaxone (to which the organism was susceptible) on April 1. Tissue cultures from the necrotic heel yielded *Pseudomonas aeruginosa* sensitive only to imipenem. Although fever was lower after 1 day of ceftriaxone, the patient's medication was switched to IV imipenem on April 2. He remained afebrile thereafter.

On April 1 (6 days after the patient's first spike of temperature), three healthcare workers from the ward into which he had first been admitted became febrile. At this time, physicians were notified that the patient was on a surveillance program for SARS. He was transferred from the general surgical ward to an isolation room, and healthcare workers used a combination of airborne, contact, and droplet precautions. His clinical course was scrutinized for evidence of SARS. Despite the positive contact history, he did not have any respiratory symptoms. Three chest x-rays performed on days 1, 5, and 7 of hospitalization were normal (Figure 1A, B, and C). The fever could have been attributed to the *E. coli* bacteremia because it subsided after the patient's antimicrobial drug was changed to an appropriate one. Over the subsequent days, 16 healthcare workers from the two wards where this patient was treated became febrile.

On day 11 of hospitalization (April 3, 14 days after the patient's last day in Tan Tock Seng Hospital), an ill-defined air space shadow was noted in the right lower zone

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Table. Laboratory results for SARS patient[a]

Characteristic	March 24	March 25	March 28	March 30
Hemoglobin (g/dL)	5.6	7.5	9.4	10.9
Leukocyte count ($x10^9$/L)	11.3	8.99	8.39	10.07
Polymorphs (%)	79.3	83.0	77.3	81.4
Lymphocytes (%)	11.4	8.1	14.3	13.8
Monocytes (%)	8.1	5.3	8.2	4.5
Eosinophils (%)	1.1	0.6	0.1	0.1
Basophils (%)	0.1	0.3	0.1	0.2
Platelets ($x10^9$/L)	421	459	332	286

[a]SARS, severe acute respiratory syndrome.

of his chest x-ray (Figure 2). On May 5, he was transferred back to Tan Tock Seng Hospital, an officially designated SARS hospital. The patient had no further temperature spikes and no respiratory symptoms, despite the chest x-ray abnormalities. Respiratory distress did not develop, and neither methylprednisolone nor ribavirin was given. The patient completed a course of imipenem but remains in hospital at the time of writing because of nosocomial sepsis. On April 8, his brother was also admitted to Tan Tock Seng Hospital for acute respiratory failure and died.

Throat swabs from our patient were collected on April 4 and stool samples were collected on April 10, days 9 and 15 after the onset of fever, respectively. These samples were sent for viral studies that included virus isolation and reverse transcriptase–polymerase chain reaction (RT-PCR) for the SARS-associated coronavirus (SARS-CoV). Three sets of primers were used. The first two sets were SAR1S/As and BNIoutS2/As as described in the paper by Drosten et al. (7); the third primer set was Cor1/2 (5'-CAC CGT TTC TAC AGG TTA GCT AAC GA-3' and 5'-AAA TGT TTA CGC AGG TAA GCC TAA AA-3') from the Government Virus Unit, Hong Kong.

From the throat swab, a weak band measuring 310 bp was found by using the Cor1/2 primer set only. Positive bands were seen with all three primer sets on the stool sample; the bands with the SAR1S/As and BNIoutS2/As primers measured 190 and 150 bp, respectively.

The diagnosis of SARS in the patient's brother was subsequently confirmed on April 9 when a throat swab was positive for SARS-CoV by PCR. Multiple postmortem samples were also positive for SARS-CoV by PCR, and SARS-CoV was also isolated in the lung tissue.

Serum samples from the patient and the healthcare workers who were his contacts were tested for total antibodies to SARS-CoV with an enzyme immunoassay by using SARS-CoV Vero E6 cell lysate that had been developed by the Centers for Disease Control and Prevention. Results of serologic testing were positive at day 41. Serum samples were taken from 14 of the 16 healthcare workers at least 21 days after onset of symptoms. Of these, 13 were positive for antibodies to SARS-CoV.

Extensive epidemiologic studies identified this patient as the common source for the cluster of healthcare workers in Singapore General Hospital who were subsequently diagnosed with SARS. These healthcare workers were infected before chest infiltrates developed and the patient was isolated.

A total of 16 healthcare workers (13 nurses, one health attendant, one radiographer, and one doctor), 12 patients, and eight visitors (including his brother) from the wards in which the patient was admitted were eventually diagnosed with probable SARS. In addition, he was linked to a cluster of five healthcare workers (one radiographer and four health attendants), one visitor, and three outpatients at the diagnostic radiology department where he had barium studies and an ultrasound performed.

Epidemiologic evidence suggested that this patient was the source for this cluster. He was linked to one of the index cases in Tan Tock Seng Hospital, had the earliest onset of fever among the cohort of Singapore General Hospital probable cases, and was the only infected patient who had been in the two wards during the relevant time period. In addition, all the nurses infected had been assigned to care for him during the incubation period of their illness. Strong supportive evidence that could not otherwise be explained by contact with other patients comes from the cluster from radiology department.

Conclusions

We present this case to highlight the diagnostic as well as public health problems posed by a patient with a rather atypical SARS, whose illness was easily explained by a positive blood culture. Classically, SARS is described as an illness with an incubation of 2 to 7 days followed by a prodrome of high fever with headache, malaise, and myalgia. At the onset of the illness, some patients have mild respiratory symptoms. After 3 to 7 days, a lower respiratory phase with nonproductive cough or dyspnea begins (8). Although the clinical signs and symptoms in otherwise healthy persons are widely known, the full clinical spectrum is not known.

In the study by Lee et al., 78% of patients had abnormal chest radiographs at the onset of fever (4). Peiris et al.

reported that all their patients had radiologic evidence of consolidation at admission (9). In another study of 10 cases, 9 had abnormal chest x-ray results (3). A Canadian study reported that two of nine patients had subtle chest radiographs. Repeat chest x-rays were read as normal in these two patients (2). Without radiographic abnormalities, the diagnosis of SARS can be difficult, especially if a cause for fever exists. By the time the radiographs became abnormal in our patient, he had infected healthcare workers. The implications of such a case and its consequences on the practice of medicine are important, even in current SARS-free areas because of world travel.

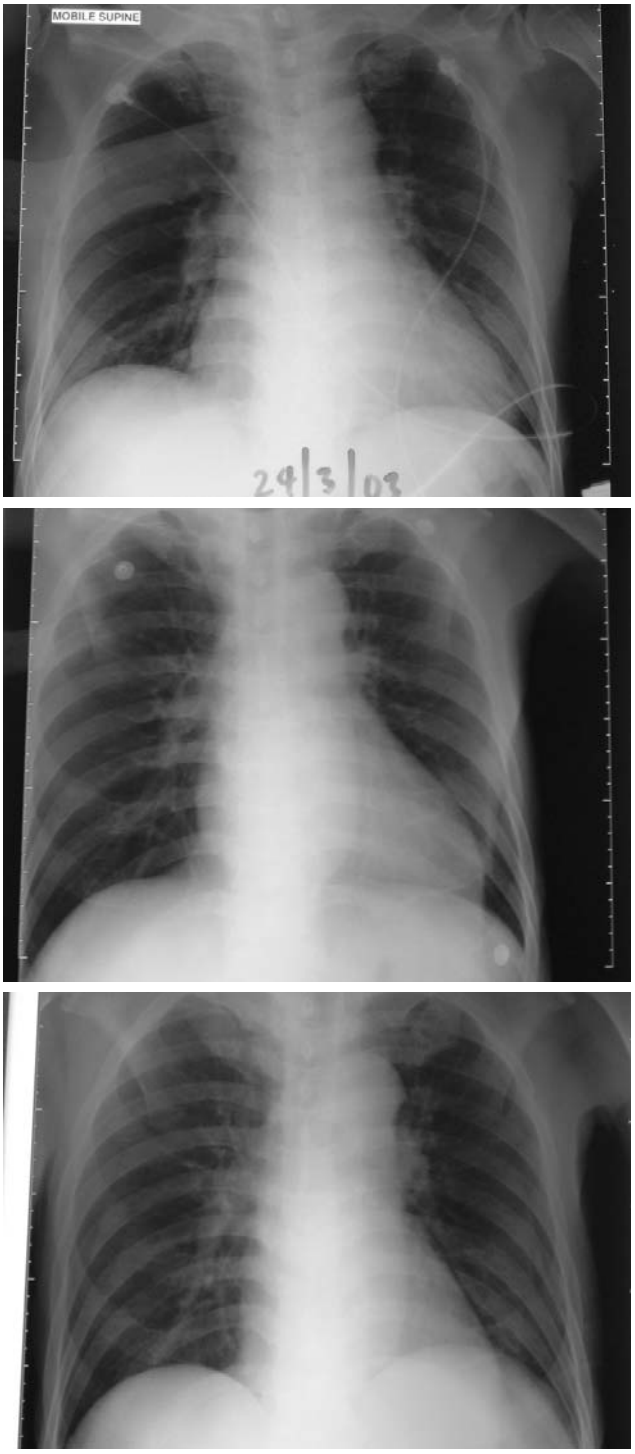

Figure 1. A, radiograph on admission; B, radiograph on day 5 of hospital stay; C, radiograph on day 7 of hospital stay.

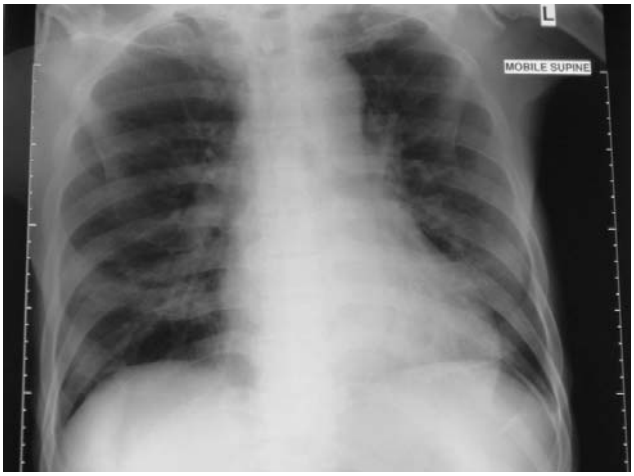

Figure 2. Radiograph on day 11 of hospital stay (day 14 after contact with a SARS patient).

Although we are taught to apply Occam's razor and search for a unifying diagnosis, multiple coexisting conditions are a part of clinical medicine. SARS can coexist with other febrile illnesses. The combination of atypical signs and symptoms and a coexisting diagnosis can have negative public health implications.

Close contact is defined by WHO as having cared for or lived with a SARS patient or having had direct contact with respiratory secretions and body fluids of a SARS patient. This contact history is often difficult to determine and quantify. In one case, the only "contact" elucidated was passing through an emergency department of a hospital with a SARS outbreak (10). We are not the first group to have seen atypical SARS in a patient with multiple coexisting conditions (10).

In a SARS outbreak, we suggest that all patients with undifferentiated fever or pneumonia be cared for as if they had SARS for the safety of healthcare workers and patients, implying the use of full precautions (N95 respirators, gown, gloves, and goggles) by healthcare workers for all patient-care activities (e.g., ward rounds, baths, wound dressings, performance of radiologic procedures). A powered air purifying respirator should be used when performing aerosol-generating activities, e.g., chest physiotherapy. Patients with undifferentiated fever or pneumonia should be placed in single rooms that meet generally accepted guidelines for the isolation of infected persons (11). Establishing an explanation for the fever (e.g., a positive blood culture) in a person with a contact history should not

necessitate removing the patient from isolation when a SARS outbreak is ongoing. A detailed contact history should include the travel history of the patient and his family members, as well as of their medical condition, and a much broader definition of contact is necessary, e.g., being in a hospital in which a SARS outbreak occurs. Tests for the SARS-CoV may be ordered, but their low sensitivity must be considered when deciding on the patient's disposition.

Extreme measures, such as regarding all patients with respiratory infections as potential SARS cases, have also been advocated in other studies (12). Nebulizer therapy has been banned in many institutions in Hong Kong, and a protocol for delivering inhaled bronchodilators without nebulization to patients with asthma has been implemented in Singapore General Hospital. Issues, such as bed availability, will need to be weighed against the need to keep patients in isolation rooms. The number of patients that can be cared for will also be lower. The SARS outbreak has focused attention on hygiene standards in our hospitals. Asymptomatic or pauci-symptomatic cases are the norm with most viral infections. With SARS, such patients may still be highly infectious. Infection control measures are needed to prevent similar clusters of infections in the future.

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HHS/CDC Legal Response to SARS Outbreak

James J. Misrahi,* Joseph A. Foster,* Frederic E. Shaw,* and Martin S. Cetron*

Before the severe acute respiratory syndrome (SARS) outbreak, the Centers for Disease Control and Prevention's (CDC) legal authority to apprehend, detain, or conditionally release persons was limited to seven listed diseases, not including SARS, and could only be changed using a two-step process: 1) executive order of the President of the United States on recommendation by the Secretary, U.S. Department of Health and Human Services (HHS), and 2) amendment to CDC quarantine regulations (42 CFR Parts 70 and 71). In April 2003, in response to the SARS outbreak, the federal executive branch acted rapidly to add SARS to the list of quarantinable communicable diseases. At the same time, HHS amended the regulations to streamline the process of adding future emerging infectious diseases. Since the emergence of SARS, CDC has increased legal preparedness for future public health emergencies by establishing a multistate teleconference program for public health lawyers and a Web-based clearinghouse of legal documents.

Under our American constitutional structure, the "police power" (the authority of sovereign governments to enact laws and promote regulations that safeguard the health, safety, and welfare of its citizens) is reserved to the states by the 10th Amendment to the U.S. Constitution, while the federal government exercises authority to regulate interstate and foreign commerce (1). As a result, state and local health departments have primary responsibility for controlling communicable diseases within their boundaries, while the federal government is primarily responsible for controlling transmission and spread of communicable diseases from abroad and from one state to another. Rapidly spreading epidemic diseases, such as severe acute respiratory syndrome (SARS), have the potential to cross interstate and international borders, potentially overwhelming the ability of any one jurisdiction to respond, despite the appropriate efforts taken by health officials. Recognizing the cross border nature of some communicable diseases and in light of this nation's constitutional structure, section 361 of the Public Health Service Act (42 United States Code section 264) authorizes the Health and Human Services (HHS) Secretary to make and enforce regulations necessary to prevent the introduction, transmission, and spread of communicable diseases from foreign countries into the United States and from one state or possession into another.

In enacting section 361, Congress recognized "the impossibility of foreseeing what preventive measures may become necessary" (2). Accordingly, Congress quite logically delegated to the executive branch the responsibility of designating specific communicable diseases that would be subject to federal isolation and quarantine measures. As enacted in 1944, the statute required the President to list the diseases for which quarantine was authorized through executive order, on recommendation of the HHS secretary and a group known as the National Advisory Health Council (2). The first executive order listing "quarantinable" diseases was issued by President Truman on March 26, 1946 (3). Presidents Eisenhower, Kennedy, and Reagan issued successive orders in 1954, 1962, and 1983, respectively (4–6). The quarantinable diseases listed in these executive orders were published in regulations found in 21 Code of Federal Regulations (CFR) Part 1240 and 42 CFR Part 71.

Historically, two sets of regulations promulgating section 361 have existed: one designed to prevent the introduction, transmission, and spread of communicable diseases from foreign countries into the United States and the other designed to prevent the interstate movement of communicable diseases within the United States. The Centers for Disease Control and Prevention (CDC) had administered the foreign quarantine regulations, while the U.S. Food and Drug Administration (FDA) had administered the interstate quarantine regulations. In addition to quarantine, these regulations authorize a variety of other public health measures, including reporting of ill passengers onboard international conveyances, sanitary inspection of arriving vessels and cargo, and restrictions on articles or imports that may be sources of infection to human beings. On August 16, 2000, FDA transferred a portion of its

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domestic quarantine authority (the portion dealing with persons) to CDC, while retaining its authority to control animals and other products that may transmit or spread communicable diseases (7). The portion of FDA's regulations dealing with persons appearing in 21 CFR Part 1240 was transferred and recodified in CDC's regulations at 42 CFR Part 70 (7). This transfer reduced potential delays in implementing quarantine by consolidating authority to quarantine persons with specified communicable diseases under one federal agency.

As part of its planning for bioterrorism and especially in light of the events of September 11, 2001, HHS sought to further expedite quarantine procedures by reducing potential delays involved in adding new diseases to the list of quarantinable diseases. On June 12, 2002, President Bush signed into law the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, which, among other things, eliminated the need to convene an advisory committee to amend the list of diseases (8). The 2002 legislative changes also clarified that federal isolation and quarantine measures apply not just to persons who are infectious but also to persons who have been exposed to a communicable disease and may potentially become infectious (8).

HHS/CDC Legal Response

Before the outbreak of SARS, the list of federal quarantinable diseases in the United States had not been revised since 1983. It included cholera, diphtheria, infectious tuberculosis, plague, smallpox, yellow fever, and viral hemorrhagic fevers such as Marburg, Ebola, and Congo-Crimean (4–6). Within days of the appearance of SARS, other countries, including Canada, Hong Kong Special Administrative Region, and Singapore instituted restrictive health measures, including large-scale quarantine, to prevent the further spread of the disease. In Ontario, Canada, where SARS-associated coronavirus (SARS-CoV) was transmitting in the population, the provincial government made SARS a reportable, virulent, communicable disease under Ontario's Health Protection and Promotion Act. This change enabled Ontario public health officers to issue orders to enjoin infected persons from engaging in activities that may transmit SARS. At the federal level, Health Canada also dispatched quarantine officers to international airports in Toronto and Vancouver, screened incoming air passengers from infected areas for SARS, and distributed health alerts at major airports in Canada.

In the United States, the federal executive branch moved rapidly to revise the list of quarantinable communicable diseases by adding SARS to the diseases specified in the April 4, 2003, executive order (9). This provided U.S. federal health officials with quarantine powers comparable to those in other countries affected by SARS. Similar to actions taken in other countries, CDC quarantine officers also began screening incoming passengers for symptoms of SARS, distributing health alerts and advisories regarding SARS, and coordinating with airport personnel in the evaluation of sick passengers. Meanwhile, the nature of the disease was rapidly evolving. For example, it was not known whether the name of the disease might change from SARS to something else as more was learned about the disease. To deal with this possibility, the executive order described SARS as follows: "a disease associated with fever and signs and symptoms of pneumonia or other respiratory illness, is transmitted from person to person predominantly by the aerosolized or droplet route, and, if spread in the population, would have severe public health consequences" (9). HHS also streamlined the process of adding new quarantinable diseases by eliminating the need to dual-publish the list of diseases in an executive order and in regulations (10). Future revisions to the list of quarantinable diseases require only an executive order, which will be posted on the Web at: http://www.cdc.gov and http://www.archives.gov/federal_register (10).

CDC has generally deferred to state and local health authorities in the primary use of their own separate "police power" quarantine authorities to restrict the movement of persons within their boundaries. During the SARS outbreak, for example, some states relied on their own legal authorities to control the movement of persons, so it was not necessary for CDC to invoke federal quarantine power to compel the isolation or quarantine of a person within a state. On the basis of a long and successful history of collaboration with the states during public health emergencies, CDC is likely to invoke federal quarantine power only rarely, such as at ports of entry or other time-sensitive situations. In these situations, and in others that are, for example, inherently and necessarily beyond the capacity of state and local jurisdictions to control, CDC has the legal tools it needs to quarantine and isolate persons for SARS and other specified communicable diseases.

Future Action

While this country was fortunate in that SARS did not reach the scale of the outbreak in Toronto or Singapore, a lesson learned from the outbreak is that federal, state, and local officials will have to work closely in coordinating quarantine actions at all levels of government. Historically, public health legal counsels have served as "technicians" in public health practice, asked by the public health agencies they serve to interpret arcane statutory language and render opinions. Legal preparedness, however, is increasingly being viewed as a critical component of state and local government public health preparedness activities. As demonstrated repeatedly, in the SARS outbreak (quarantine/isolation); in the introduction of monkeypox in the

Western Hemisphere (restrictions upon the exotic animal pet trade); and during West Nile virus season (mosquito abatement/spraying programs), legal issues are nearly always intertwined with public health responses. During emergencies, communication among public health lawyers at all levels (federal, state, and local) is a crucial part of the "new normal" in public health. Until recently, however, there was no ready means for public health lawyers to communicate rapidly among themselves and quickly access relevant legal information.

During the SARS outbreak, CDC established a series of telephone conferences, whereby federal, state, and local public health lawyers could discuss important legal issues of the day and trade ideas about pending legal problems. These teleconferences were particularly useful in exchanging information concerning the interplay of quarantine authority at the federal, state, and local levels and discussion of procedural requirements involved in executing isolation or quarantine orders. These legal teleconferences were reinstituted and held daily during the peak of the monkeypox outbreak. Additionally, during the monkeypox outbreak, CDC developed a Web-based clearinghouse where just-issued legal documents such as gubernatorial executive orders and state and local health department rules could be posted. CDC, through its Public Health Law Program, plans to expand the scope of this clearinghouse to reduce the time required to identify relevant legal documents and disseminate them to public health legal counsels on a "real time" basis. The clearinghouse is available at: http://www.phppo.cdc.gov/od/phlp/. The addition of a Web-based clearinghouse and a teleconference capacity increases CDC's effectiveness in responding to public health emergencies by more fully integrating lawyers into the public health response.

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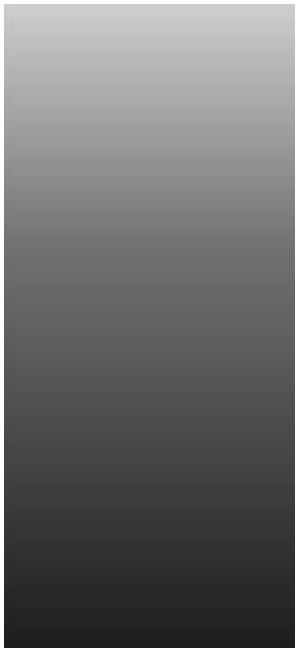

Making State Public Health Laws Work for SARS Outbreaks

Edward P. Richards* and Katharine C. Rathbun†

In their article, HHS/CDC Legal Response to Outbreak of Severe Acute Respiratory Syndrome (SARS), Misrahi, et al. (1) describe the updated federal laws and response plans for handling SARS and related communicable diseases. Federal authority is important to control the interstate and international movement of persons who are potentially infectious, but most isolation and quarantine orders will be performed by state and local officials, using state and local law. We discuss how existing laws might be modified to facilitate effective SARS control while providing legal protections to restricted persons.

Traditional Powers

The drafters of the U.S. Constitution gave states broad powers to control communicable diseases because the colonies were ridden with malaria, yellow fever (2), cholera, and typhoid. States exercised these powers as necessary, quarantining persons and even whole cities and regions (3). This public health authority has been upheld by the U.S. Supreme Court in all cases (4), except when it is was clearly a subterfuge for racial discrimination (5), and in 1950, every state and local health department had clear powers to conduct case-finding and isolate or quarantine persons who represented a potential public health risk (6).

State public health laws do not need to be detailed and specific, but they can give public health agencies the general authority to protect the public's health and safety. Consistent with the Constitution, courts allow government agencies to fill in the details of these laws (7). Statutes do not need specific judicial review because all detentions are reviewable through habeas corpus proceedings. Habeas corpus is a fundamental part of Anglo-American law, protecting persons against illegal detention. A part of the U.S. Constitution, habeas corpus needs no additional statutory authorization, although all states provide for it.

Persons detained by the state may file a habeas corpus petition and demand that a court review their detention. In the case of quarantine due to disease, a judge would determine whether the state has shown that the detained person deserves quarantine. The judge must defer to public health authorities on their choice of public health strategies (8). Public health orders get the most permissive judicial review, the rational relationship test, because they are based on objective criteria, are usually of limited duration, and are necessary to prevent imminent harm (9).

Contemporary Public Health Laws

With the advent of AIDS in the 1980s, some civil libertarians argued that the old public health laws were outdated and no longer enforceable. There was no judicial support for this argument then (10), and today's courts are even more supportive of state powers to protect the public. Nonetheless, many states rewrote their isolation and quarantine laws to provide varying levels of mandatory judicial review, in some cases requiring that a person be provided counsel and an opportunity for a trial before detention. Such proceedings take so much time and money that they make it almost impossible to impose quarantine (11).

Even public health laws rewritten in the wake of the 9/11 events often include judicial review provisions that would be unworkable in a large outbreak; persons would either be detained illegally or be released because of legal technicalities. Improperly detained persons can sue, and these lawsuits will probably not be barred by the immunity provisions in emergency public health laws. Improperly released persons will nullify the disease control plan.

Administrative Law Solution

The best way to balance public protection with private rights is to use administrative hearings rather than judicial hearings to review quarantine and other public health orders. Administrative review is used routinely in state and federal agency proceedings, including for mental health commitments in Maryland (12). Courts have required more due process for mental health commitments than for quarantines; this difference is strong evidence that administrative review would be an acceptable alternative for public health orders. Such reviews can be appealed to the courts,

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but having the agency do the first review makes a factual record that allows quick and efficient judicial review. A petitioner can be required to go through an agency appeal before a habeas corpus review by the courts (13).

Persons who want to contest their isolation orders could be required to petition the decision maker doing the reviews. This petition could be to a health agency staff member or an appointed board. The health agency would present the basic information, and the petitioner could supply additional information in writing. Telephone interviews could be used to allow personal statements without the danger of in-person testimony. The decision maker would make a brief, written ruling based on predefined classifications. This ruling could be reviewed by an agency appeals board and would greatly simplify any subsequent appeal to the courts (14). If such a process is adopted, the statutory language to implement these reviews should be kept general to allow flexibility in the face of different epidemic conditions.

Such a review should also be part of the quality assurance for isolation and quarantine orders. A key part of any isolation and quarantine process for SARS would be thorough recordkeeping of all orders, whom such orders apply to, their duration, and the disease outcome in each case. There should be administrative oversight to ensure that the orders are proper and that other necessary actions are carried out, such as providing food and medical services to restricted persons.

Conclusions

A major SARS outbreak would stretch many state and local public health laws to the breaking point. These laws should be reviewed and rewritten as necessary. Fair process can be based on sound administrative law principles that dramatically reduce the role of judicial review in isolation and quarantine orders.

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Fear and Stigma: The Epidemic within the SARS Outbreak

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Because of their evolving nature and inherent scientific uncertainties, outbreaks of emerging infectious diseases can be associated with considerable fear in the general public or in specific communities, especially when illness and deaths are substantial. Mitigating fear and discrimination directed toward persons infected with, and affected by, infectious disease can be important in controlling transmission. Persons who are feared and stigmatized may delay seeking care and remain in the community undetected. This article outlines efforts to rapidly assess, monitor, and address fears associated with the 2003 severe acute respiratory syndrome (SARS) epidemic in the United States. Although fear, stigmatization, and discrimination were not widespread in the general public, Asian-American communities were particularly affected.

Public health strategies that deal with rapidly evolving disease outbreaks of new and emerging infectious diseases require a delicate balance between protecting the public's health and initiating exclusionary practices and treatments that can lead to fear and stigmatization of, and discrimination against, specific populations. The outbreak of severe acute respiratory syndrome (SARS) illustrates these difficulties. SARS spontaneously appeared in the southern province of Guangdong, People's Republic of China, in November 2002 (1,2). By July 2003, the epidemic, had spread to more than 30 countries with 8,427 cumulative probable cases and 916 deaths and was identified as a global threat to health (1). In the United States, 418 cases were reported with 74 classified as probable SARS; no deaths occurred (1). As with many disease outbreaks, scientific information and data related to the disease changed almost hourly, as public health scientists and practitioners responded to the worldwide outbreak, which was coupled with widespread fear (3,4).

SARS-related Fear, Stigmatization, and Discrimination

While persons, agencies, and governments sought to identify modes of transmission, strategies for disease containment, and treatment for SARS, fear spread unchecked throughout the global community. Fear of SARS arose from the underlying anxiety about a disease with an unknown cause and possible fatal outcome (5). Stigmatization of potential SARS patients emerged early in the outbreak, as global media reported dramatic stories from Asia in print media, television, and the Internet. Headlines from the English-language press heightened the fear. "Concern is mounting over the continuing spread of the deadly SARS virus. Some experts say it could have a similar impact to the 1918 flu epidemic that killed 50 million—or the current world HIV crisis," wrote the British Broadcasting Corporation from London, England (6). "China has threatened to execute or jail for life anyone who deliberately spreads the killer SARS virus," stated the Cable News Network from Beijing, China (7).

Studies have shown that during serious disease outbreaks, when the general public requires immediate information, a subgroup of the population that is at potentially greater risk of experiencing fear, stigmatization, and discrimination will need special attention from public health professionals (8–10). The recent SARS outbreak was a classic example of such an outbreak.

Fear is further fueled when infection control techniques and restrictive practices such as quarantine and isolation are employed to protect the public's health (11,12). While exclusionary practices based upon the best available scientific evidence may be scientifically and ethically sound for one population, those same practices may not be sound for all populations (5,11). During the SARS outbreak, some persons became fearful or suspicious of all people who

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looked Asian, regardless of their nationality or actual risk factors for SARS, and expected them to be quarantined. Some Americans did not understand that quarantine and isolation practices appropriate for SARS-affected areas in Asia, where community transmission was a concern, were practices that were not appropriate in the United States where the disease was not community acquired. For example, some persons, who had recently traveled to areas where SARS was spreading, isolated themselves, even though they had no symptoms and had not been exposed to someone with SARS.

Mitigating Fear, Stigmatization, and Discrimination through Strategic Community Outreach

Fear of being socially marginalized and stigmatized as a result of a disease outbreak may cause people to deny early clinical symptoms and may contribute to their failure to seek timely medical care (5). Such fear can ultimately increase stigmatization when cases are identified at a later date (11). Stigmatization associated with discrimination often has social and economic ramifications that intensify internalized stigmatization and feelings of fear (13).

Containing fear, which is integral to the public health management of a new and emerging disease such as SARS, is best accomplished by a behavioral strategy that addresses the needs of a segment of the population at risk of becoming stigmatized and discriminated against. This strategy works best as a complement to a larger public health education and communication campaign. Typically during outbreaks, initial risk communication is targeted to frontline public health professionals through vehicles such as the Morbidity and Mortality Weekly Report. Initial communication provides information on case definitions and laboratory-testing strategies, as well as interim guidelines for infection control and other critical issues. Communication strategies for the general public most frequently involve television sound bites, press conferences with dignitaries and health officials, and targeted release of information to mass media outlets such as newspapers and Internet sites (14). Although these risk communication activities are critical for keeping the general public informed during an outbreak, they can fail to meet the personal needs of the affected population and the general public.

Methods

During the first week of April 2003, the National Center for Infectious Diseases (NCID) at the Centers for Disease Control and Prevention (CDC) formed a 14-member, multidisciplinary NCID/SARS Community Outreach Team as part of its emergency response to the global SARS outbreak. While other NCID/CDC response teams dealt with laboratory investigations, surveillance, communication, and clinical infection control practices, the Community Outreach Team worked to implement rapid public health strategies to document, monitor, and assist in ameliorating specific problems associated with fear, stigmatization, and discrimination attributed to the SARS outbreak in the United States.

In creating a rapid public health intervention to mitigate behaviors and practices associated with SARS-related fear, the team recognized the need to address the experiences of persons at greatest risk for experiencing SARS-related fear, stigma, and discrimination. The team monitored stigmatizing ideas and behaviors in the general population and the media, particularly toward Asian Americans, who were disproportionately reporting fear, stigmatization, and discrimination compared to the general public. The team began working with Asian-American communities to develop a culturally tailored intervention that 1) promoted community understanding of the facts related to the transmission and prevention of SARS; 2) contributed to the strengthening of community resiliency and capacity to mitigate fear, stigmatization, and discrimination; and 3) encouraged appropriate health-seeking behaviors for those who may have been exposed to SARS and were experiencing early symptoms. The team also worked to dispel myths; keep the general public better informed; prevent discrimination against SARS-affected communities; and provide guidance for institutions, agencies, and organizations hosting international visitors from SARS-affected countries.

Rapid Situational Assessment

During the first 3 weeks of April 2003, the NCID/SARS Community Outreach Team conducted a rapid situational analysis to determine the impact of SARS-related fear, stigmatization, and discrimination within the Asian-American community in the United States. The team carried out the following activities: 1) facilitated group discussions with key opinion leaders within the Asian community in the United States; 2) collected and monitored the CDC Public Response Service data; 3) collected and monitored Asian-language newspapers, Internet sites, and other information sources; 4) reviewed polling data and other communication information; 5) conducted community visits, panel discussions, and media interviews; 6) solicited information from state and regional minority health liaisons nationwide; 7) developed ongoing relationships with the Asian-American communities; particularly in major metropolitan areas throughout the United States; and 8) determined new data-gathering strategies as needed.

Group Discussions

The team conducted group interviews through teleconferences with national, state, and local influential leaders

in the Asian-American community throughout the United States. The team also conducted group interviews with chambers of commerce and trade association members, school officials and representatives, state public health department staff, academicians at universities, mental health professionals, and others. The 11 teleconferences the team conducted reached more than 70 persons who represented more than 50 agencies, organizations, and communities. The goals of the group interviews were the following: 1) determine the impact of SARS-related fear on the Asian community; 2) document examples of fear, stigmatization, and discrimination; 3) determine strategies for identifying and reaching "hidden populations"; 4) develop partnerships with leaders and community members of the affected populations; 5) determine the needs of affected populations; and 6) respond appropriately to those needs through a targeted intervention with activities and Asian-language materials.

Five major recommendations were derived from the facilitated group discussions with key informants: 1) develop simple, tailored SARS prevention messages; 2) develop SARS information materials in various Asian languages; 3) disseminate SARS information through multiple and culturally appropriate channels, including (but not limited to) community visits, town hall meetings, and health education and communication channels to complement mass media messages; 4) establish partnerships with local Asian-American community–based organizations to educate the community; and 5) ensure that CDC would continue to provide leadership and coordination in preventing and controlling SARS. The relationships developed during these group discussions allowed team members to monitor and document ongoing stigmatizing situations related to the disease outbreak in real time and to deal more effectively with intentional and unintentional discrimination.

CDC Public Response Service

CDC operates the Public Response Service (CDC PRS) under contract with the American Social Health Association. This contract provides hotline service to the general public requesting information via telephone and email about bioterrorism and other disease emergencies, including SARS. The NCID/SARS Community Outreach Team worked with the CDC PRS to track a daily sample of incoming SARS-related calls, specifically noting questions associated with fear, stigmatization, and discrimination directed toward the Asian-American community. This system allowed the team to help determine specific answers to frequently asked questions for hotline staff and to develop simple, prerecorded Asian-language messages. Passive data collection of SARS fear-related concerns began on April 29, 2003. During May 2003, 7,327 SARS-related calls were received; 4,013 (54.7%) of these calls were passively sampled. Of these sampled calls, an average of 10% of callers expressed concerns related to fear, stigmatization, and discrimination. A caller could express more than one concern. Major concerns included the following: fear of buying Asian merchandise (187 calls); working with Asians (83 calls); living near Asians (45 calls); going to school with Asians (41 calls); and more generic issus such as being on a cruise ship or airplane (77 calls); and church, school, or workplace issues (65 calls). Most SARS calls related to transmission, symptoms, and treatment of disease and travel advisories.

Asian-Language Information Sources

One critical component of the team's activities was determining where members of the Asian-American community were getting SARS-related information. Team members monitored English-language and Asian-language electronic, print, and television media coverage and informal chat rooms in the United States and other countries to stay abreast of changing information about the nature of the SARS outbreak that could influence fear, stigmatization, and discrimination. The assessment showed that many people within the Asian-American community were getting information from Asian-language newspapers, television, and Internet sites directly from China, Hong Kong, Taiwan, and other Asian areas—usually hours ahead of information providers in the United States. The information provided by these Asian-language sources was often inconsistent with newspaper, television, and Internet coverage in the United States, thus creating fear and suspicion that the United States government might not be telling the truth about the outbreak in this country. Independent content-analysis research conducted by InterTrend Communications (San Francisco, CA) compared four of the most popular Chinese language newspapers in the United States with two popular national mainstream English-language newspapers from March 21 to April 3, 2003 (15). InterTrend data showed that 1) Chinese-language newspapers were more likely to highlight SARS news related to the Chinese community in the United States or from China more prominently than mainstream English-language newspapers; and 2) Chinese-language newspapers were more likely to have articles on SARS, including featured in-depth articles, than mainstream English-language U.S. national newspapers (15). These findings supported the team's initial assessment (based on an informal convenience sample of Asian-language papers).

General email inquiries sent to the CDC communications center and information from public health professionals, health providers, and community members led the team to SARS-related Internet sites that contained rumors and inaccurate information, which added to general misunderstanding, confusion, and fear. Even legitimate public

health Internet sites from different parts of the world provided disparate information as the outbreak unfolded, furthering uncertainty and fear in the United States. The team also monitored Internet sites that supported community fears as they promoted home remedies, medicinal cures, and inappropriate and unnecessary protective equipment. Monitoring the information sources of the affected population was a critical activity, allowing the team to separate fact from fiction with accuracy and timeliness and address salient issues and concerns during community visits.

Results

Rapid Situational Response

Based on its rapid situational assessment, the team was able to develop interventions to assist in mitigating fear, stigmatization, and discrimination. Team members carried out the following activities: 1) advised other SARS emergency response teams on how to minimize the risk of stigmatizing groups in their own communications by focusing messages on the virus and the relevant behavioral risk factors; 2) assisted with developing culturally tailored health education materials; and 3) conducted community visits, panel discussions, and media interviews to positively influence negative behaviors occurring in communities. These visits and other contacts with the Asian-American community allowed CDC to develop ongoing relationships and helped the team determine new data-gathering strategies.

Targeted Health Education Materials

During a disease outbreak, information changes rapidly as scientific evidence is collected and analyzed. Vital components of the team's activities were prioritizing and translating existing information and guidance documents and developing health education materials to address the specific needs of the Asian-American community. An in-house translation service did not exist, and the rapidly evolving scientific evidence challenged the turnaround time for developing, translating, and disseminating information. The team worked to identify priority documents for translation and to ensure Asian-language translation for Web and print products tailored to the Asian-American community. To ensure accurate translations, CDC contracted with professional translation services and had all documents back-translated. Web-based information on SARS included documents in traditional Chinese, simplified Chinese, Korean, Vietnamese, and Japanese, as well as French and Spanish. The team also created brief, recorded educational hotline messages in Chinese and Vietnamese. The main messages for people in the United States were the following: 1) the risk of SARS is low; 2) severe cases of SARS have been uncommon, and there have been no deaths in the United States; 3) methods for disease prevention in the general public are like those of other viral diseases; and 4) although no evidence of community spread currently exists, continued vigilance, aggressive case management, and infection control are needed.

Community Field Visits

Team members conducted field visits to Asian communities in Boston; New York City; Oakland, California; San Francisco; Washington, D.C.; Edison, New Jersey; and Los Angeles to respond to the direct needs of the communities and gather information. The team met with community leaders, toured the communities, informally gathered further information, and gave community SARS presentations in seven cities, reaching approximately 500 persons. Through community visits, the team was able to 1) provide the latest in evidence-based information on SARS with Asian-language education materials; 2) dispel misconceptions, myths, and rumors; 3) act as a catalyst for bringing together a broad spectrum of organizations and persons in the community to create local networks to promote community resiliency; and 4) provide credibility and reassurance to those who felt vulnerable. Speakers also presented a public health model for mitigating fear, stigmatization, and discrimination that could be instituted by public health officials, clinicians, and community members. Through open discussion sessions and informal information gathering in the community, the team found that SARS-related stigmatization was occurring more frequently within the Asian community than from outsiders directed toward the Asian community. The team also found that those persons with SARS-like symptoms who used traditional herbal physicians and pharmacies were less likely to be referred to, or seek out, public health officials, suggesting that further research into strategies to reach this population is needed. Conducting community visits also showed that CDC was responding to the needs of the community at risk for SARS-related fear, stigmatization, and discrimination and was modeling positive behaviors to the public.

Discussion

Other infectious disease epidemics have been associated with specific ethnic groups. Fear, stigmatization, and discrimination plagued Russian Jewish immigrants when the 1892 outbreaks of typhus fever and cholera in New York City were traced to Russian Jewish immigrants from Eastern Europe (8). In the spring of 1900, the Chinatown community in San Francisco was faced with extreme discrimination due to an outbreak of bubonic plague, the "black death," attributed to rats transported on a ship from Hong Kong (9). In 1993 an outbreak of hantavirus infection in the Four Corners area (where the borders of four states—Arizona, New Mexico, Utah, and Colorado—

meet) of the United States was initially referred to by reporters as a Navajo disease, which led to severe fear, stigmatization, and discrimination of Native Americans in the region (10). Previous scientific studies have shown that fear associated with stigmatization and discrimination has negatively affected public health efforts with chronic conditions and diseases such as mental illness, HIV/AIDS, tuberculosis, leprosy, and epilepsy (16–20). More recently, stigmatization associated with fear and the AIDS epidemic negatively influenced voluntary testing, counseling, and treatment of those infected with the disease (21). Health providers have also seen reluctance by recent refugees and immigrants to get tested and treated for tuberculosis because of possible social stigmatization (22). The potential of being labeled at-risk for having or transmitting a stigmatizing condition such as SARS creates fear and anxiety, and an entire population of people can be at risk for becoming stigmatized in society (23).

Protecting the health of the public while preventing stigmatization of segments of the population during a rapidly evolving disease outbreak is complex. The team's experience during the recent SARS outbreak demanded anticipatory insight, perceptive planning, and a rapid response to a targeted audience with specific cultural perspectives and influences. It also required us to recognize the distinctive features of SARS in a medical, social, and cultural context. Weiss states, "Preventing fear and stigmatization depends on controlling or treating the target health problem, countering tendencies of those who stigmatize others, and supporting those who are stigmatized through emotional support and social policies" (11).

The data collected during the rapid situational assessment were critical in guiding activities of the team. Both the data and the data collection process assisted the team in establishing interpersonal relationships with community leaders, determining priority needs, identifying responsible intervention strategies, and developing effective communication channels. The team was able to better understand community perceptions and attitudes by identifying the communities' trusted sources of information. When conducting community visits, the team was able to address discordant information, myths, and rumors; provide simple Asian-language messages and materials; and act as a catalyst to build community resiliency and prepare for the possibility of future emerging diseases. The team was also able to keep CDC/NCID leaders informed and to intervene when they identified discriminatory policies, practices, and actions that were inconsistent with evidence-based public health recommendations and guidelines.

Quelling fear-driven stigmatization and discrimination during the SARS outbreak required tailored intervention strategies carried out by the SARS Community Outreach Team. These activities complemented traditional risk communication for the general public. To be effective, behavioral intervention approaches, messages, and materials had to be salient for the affected population, in this case Asian-American communities within the United States. Further, these interventions aimed at promoting an accurate understanding of the epidemic both in the general population and within the affected community, that is, the dynamic nature of the outbreak and its cause, treatment options, and prevention strategies. Through interpersonal connections, the team members worked to promote reassurance and enhance community resiliency.

Public health professionals must understand the necessary balance needed to protect the public's health with appropriate exclusionary practices, while at the same time preventing fear, stigmatization, and discrimination of specific segments of the population. As we prepare for the next new or reemerging disease outbreak, we should also be preparing to deal with the fear epidemic that will likely accompany it. By developing effective behavioral and health education strategies and providing timely attention to the special needs of affected populations, we can ensure that, no matter what the infectious disease, we can limit the associated epidemic of fear and stigmatization.

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Crisis Prevention and Management during SARS Outbreak, Singapore

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We discuss crisis prevention and management during the first 3 months of the severe acute respiratory syndrome (SARS) outbreak in Singapore. Four public health issues were considered: prevention measures, self-health evaluation, SARS knowledge, and appraisal of crisis management. We conducted telephone interviews with a representative sample of 1,201 adults, ≥21 years of age. We found that sex, age, and attitude (anxiety and perception of open communication with authorities) were associated with practicing preventive measures. Analysis of Singapore's outbreak improves our understanding of the social dimensions of infectious disease outbreaks.

An outbreak of severe acute respiratory syndrome (SARS) began in Guangdong, China, on November 16, 2002. The first three SARS cases in Singapore were confirmed on March 6, 2003. By May 5, a total of 204 cases, including 27 deaths, had been confirmed. The last case was isolated on May 11, and by July 30, the end of the outbreak, 205 patients had recovered and 33 had died (1).

Since SARS infection may come from ordinary contact with acquaintances, colleagues, or strangers, outbreaks can trigger anxiety and influence public perception of susceptibility, causing serious economic and social disruption. The need for health information and for crisis management by public health authorities is also high. We examine four areas of public reaction to the SARS outbreak in Singapore: preventive practices, perception of self-health, knowledge of SARS, and appraisal of SARS crisis management.

Materials and Methods

Sample

We interviewed a representative stratified random sample of 1,202 adults (≥21 years of age). To minimize personal contact during the outbreak, participants were interviewed by telephone instead of face-to-face. The residential telephone sampling covered 90% of households in Singapore. The response rate was 62.3%, and the sampling error ±3.5% (Table 1). We used Random Digit Dialing+1, a system commonly used in public health studies, to capture unlisted telephone numbers (3).

Data Collection

We modified and expanded a structured questionnaire provided by researchers from the Department of Community Medicine, University of Hong Kong (A.J. Hedley, T.H. Tan, G.M. Leung, B.H.Y. Chan, S.Y. Ho, L.M. Ho, unpub. data). The modified questionnaire (Appendix online at http://www.cdc.gov/ncidod/EID/vol10no2/03-0418_app.htm) was translated into Mandarin, Malay, and English; interviews were conducted from May 5 to May 10, 2003. Factor analysis and logistic regression (SPSS for Windows [Version 11.5]) examined trends among four factors (SARS prevention, perception of self-health, knowledge of SARS, and perception of health authorities' crisis management). We also assessed how prevention measures correlated with other factors, including respondents' demographic characteristics.

Preventive Measures

Eight questions focused on respondents' prevention practices in the 3 days before the interview. We constructed a composite index indicating the total number (from 0 to 8) of preventive measures taken. A dichotomous indicator of preventive behavior was calculated based on the mean number of precautions taken (4.68): "low" (≤5) versus "high" (≥6).

Self-Health Perception

Three sets of questions addressed respondents' perception of their own health. The first set covered nine physical health complaints. We created a composite index of symptoms by adding all instances of health complaints over the previous 2 weeks. This index was 0 to 7 in our study since no one reported having more than seven of the nine symptoms.

The second set was a "frame of mind" index fashioned after B.A. Thyer's Clinical Anxiety Scale (4). Scores for

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Table 1. Demographic characteristics of study and total population

Characteristics	Study population No. (%) (1,201 total)	Total population[a] No. (%) (3,263,200 total)
Ethnicity		
Chinese	900 (75.0)	2,505,400 (76.8)
Malay	172 (14.0)	453,600 (13.9)
Indian	82 (7.0)	257,800 (7.9)
Other	47 (4.0)	46,400 (1.4)
Age		
21–29[b]	233 (19.0)	480,191 (20.4)
30–39	313 (26.0)	613,944 (26.1)
40–49	312 (26.0)	575,674 (24.5)
50 and older	343 (28.0)	681,282 (29.0)
Sex		
Male	599 (49.9)	1,630,293 (49.9)
Female	602 (50.1)	1,632,916 (50.1)

[a]Ref. 2., p. viii–ix.
[b]Total population figures refer to ages 20–29 years.

positive items were 1 (not at all) to 4 (very much); negative item scores were reversed, so lower total scores indicated higher anxiety. The scale had an Alpha reliability coefficient of 0.8244.

The third set addressed respondents' perceived susceptibility to SARS. Scores were 4 (very likely) to 0 (don't know). On the basis of the average score (1.5; standard deviation [SD] 1.01), we created a dichotomous variable to contrast respondents who believed they were susceptible to contracting SARS (scores 3 and 4) with those who did not (scores 0–2).

Knowledge of SARS

Three questions tested SARS knowledge. Responses were scored 0 (incorrect) or 1 (correct); a composite index indicated the number of correct answers, from none correct (0) to all three correct (3).

Appraisal of Crisis Management

Four sets of questions addressed respondents' appraisal of crisis management, but we discuss the three most relevant. The first set of five questions (Alpha reliability 0.8136) assessed opinions on information distribution. Scores were 1 (very negative) to 6 (very positive). On the basis of the mean score (4.83; SD 0.617), we calculated a dichotomous index: negative appraisal (scores $\leq$4.7) versus positive appraisal (scores $\geq$4.8).

The second set of questions addressed openness of communication. Scores were 1 (very negative) to 6 (very positive). By using the sample's mean score (4.31; SD 1.25), this variable was dichotomized into "disagreement" (scores 1–3) and "agreement" (scores 4–6).

The third set referred to the public's acceptance of quarantine regulations. The scores were dichotomized into "agreement" (1) versus "no agreement" and "don't know" (2).

Results

Responses to the survey questions are summarized in Table 2. Variables were examined by using odds ratios (ORs) at 95% confidence intervals (CI). The statistically significant ORs are reported in Table 3 with their respective level of significance from the Mantel-Haenszel common odds ratio estimates.

Recommended preventive measures were not practiced uniformly. The most practiced measures 3 days before the interview were using soap when washing hands (81%) and washing hands after sneezing, coughing, or clearing the nose (72%). The least practiced measure was wearing a mask over the mouth. A total of 4% wore masks, and most did so only when visiting a clinic or hospital or when the mask was part of a uniform (as in healthcare workers). The index of preventive measures indicates that most people (69.3%) took some preventive measures.

Respondents' perception of their health was generally positive. A relatively low proportion (22.4%) of respondents reported having any of our nine physical health complaints over the previous 2 weeks, and fewer than 1% reported the three classic symptoms of SARS (fever $\geq$38°C, cough, rapid breathing). The mean number of health complaints reported in our sample was 0.369 (SD 0.828). The survey also showed low anxiety; only 2.9% of respondents reported high anxiety. The mean anxiety score was 3.23 (SD 0.48). Most respondents (68%) thought they were not very likely or not likely at all to contract SARS, and 18% were not sure of their likelihood. Those who thought they were likely to get the disease reported slightly more anxiety. Of the three aspects of health perception, only anxiety was associated with taking precautions (OR 0.861; 95% CI 0.757–0.978). In the high-anxiety group, 34% followed six or more of the eight preventive measures, in contrast to 28% of respondents who had low anxiety.

Regarding knowledge of SARS, the sample correctly answered an average of 1.722 (SD 0.922) of 3 questions on SARS transmission. Approximately 63% answered two or more questions correctly; 11.7% did not answer any questions correctly.

Respondents had a generally high opinion of authorities' crisis management. More than 80% thought official information was accurate, clear, sufficient, timely, and trustworthy, and 72% were prepared to accept a 10-day quarantine, even in the absence of SARS symptoms or close contact with a SARS patient. Of the three crisis management aspects, one had significant influence on preventive action: respondents' opinion of authorities' openness to communication. People who thought that authorities were open to communication were more inclined to practice six or more of the eight SARS preventive measures (OR 0.909; 95% CI 0.855 to 0.966) than those who thought they had no chance to express their

Table 2. Variables used in analysis of public reaction and perspective of SARS crisis

Variable	%	Mean	SD
Symptoms (0–8) over past 2 weeks		0.3639	0.8286
None	77.6		
One or more	22.4		
Main SARS-related symptoms			
Persistent high fever ≥38°C	1.0		
Cough	9.0		
Rapid breathing	1.0		
Anxiety level		3.2307	.4819
High (1.0–2.2)	2.9		
Moderate (2.3–3.2)	42.4		
Low (3.3–4.0)	54.7		
Perceived likelihood of contracting SARS		1.5304	1.014
Very likely (4)	4.0		
Likely (3)	10.0		
Not very likely (2)	39.0		
Not likely at all (1)	29.0		
Don't know (0)	18.0		
Knowledge of SARS		1.7227	.9222
No knowledge (0 of 3 answers correct) (0)	11.7		
1 of 3 answers correct (1)	25.0		
2 of 3 answers correct (2)	42.5		
3 of 3 answers correct (3)	20.7		
Appraisal of crisis management			
"Strongly agree" and "Agree" that information by health authorities is:			
Accurate	82.2		
Clear	86.3		
Sufficient	84.5		
Timely	84.4		
Trustworthy	87.8		
Population has chance to express personal views and concerns to the authorities, "strongly agree" or "agree."	66.3		
Agreeable to 10-day quarantine after nonclose contact with SARS-infected person and no symptoms			
Agree	71.6		
Don't agree	22.4		
Don't know	6.0		
Years of formal education		10.07	3.9642
≤10 years	57.1		
≥11 years	42.9		
Practice of preventive measures		4.686	1.5286
Practicing each of eight measures "always" or "most of the time" during the past 3 days:			
Covered mouth with tissue when sneezing or coughing	62.0		
Covered mouth with bare hand when sneezing or coughing	47.0		
Washed hands after sneezing, coughing, or clearing nose	72.0		
Used soap or liquid hand-wash when washing hands	81.0		
Wore a mask	4.0		
Used serving utensils for shared food	28.0		
Took preventive measures when touching objects	15.0		
Washed hands after touching objects	48.0		
Preventive measures taken over past 3 days (score 0–8)			
Five or fewer of the eight measures	69.3		
Six or more of the eight measures	30.7		

concerns to the authorities (OR 1.434; 95% CI 1.115 to 1.846).

Three demographic characteristics were associated with taking preventive measures against SARS: sex, age, and estimated years of formal education. Women were more inclined (OR 0.770; 95% CI 0.689 to 0.861) than men (OR 1.339; 95% CI 1.166 to 1.539) to take preventive measures; this finding is consistent with other studies on health behavior in Singapore (5,6). People ≥35 years of age were more inclined to take preventive measures (OR 0.872; 95% CI 0.806 to 0.943) than their younger counterparts (OR 1.365; 95% CI 1.123 to 1.658). The association with education disappeared when controlled for sex.

Discussion

Information regarding the SARS outbreak was widely distributed by the media and government; while this information was essential to keep the public informed of the

Table 3. Practice of SARS preventive measures, 3 days before interviews

Variable	No.	OR	95% CI
Personal health evaluation			
Symptoms in past 2 weeks			
None	932	1.012	0.947 to 1.082
One or more	269	0.960	0.766 to 1.203
Anxiety[b]			
Moderate or high (score ≤3.25)	544	0.861	0.757 to 0.978
Low anxiety (score >3.25)	657	1.140	1.031 to 1.283
Perceived likelihood of SARS			
Not likely	1,034	1.031	0.979 to 1.085
Likely	167	0.833	0.621 to 1.118
Knowledge of SARS			
Two or fewer correct answers	952	1.012	0.950 to 1.079
Three correct answers	249	0.954	0.753 to 1.079
Appraisal of crisis management			
Quality of official information			
Below average (negative)	290	1.164	0.928 to 1.460
Above average (positive)	911	0.955	0.893 to 1.020
Have chance to express opinion[c]			
Disagree	271	1.434	1.115 to 1.846
Agree	930	0.909	0.855 to 0.966
Agreeable to quarantine when non-close contact with SARS-infected person and no symptoms			
Agree	860	0.969	0.899 to 1.045
Do not agree or don't know	341	1.084	0.888 to 1.323
Demographic characteristics			
Years of formal education[d]			
≤10	686	0.909	0.821 to 1.006
>10	515	1.143	0.985 to 1.325
Sex[c]			
Male	599	1.339	1.166 to 1.539
Female	602	0.770	0.689 to 0.861
Age[c] (y)			
<35	391	1.365	1.123 to 1.658
≥35	809	0.872	0.806 to 0.943

[a]SARS, severe acute respiratory syndrome; OR, odds ratio; CI, 95% confidence interval.
[b]Asymptotic significance (2-sided) ≤0.05.
[c]Asymptotic significance (2-sided) ≤0.001.
[d]Asymptotic significance (2-sided) ≤0.10.

risks for infection and preventive measures, it also could increase anxiety. However, we found low levels of anxiety in Singapore, and few reported health complaints. Reporting health complaints was not associated with taking precautions against SARS, possibly because the nine symptoms of SARS covered in our questionnaire are associated with other common diseases in Singapore (e.g., dengue fever, the incidence of which was 86.2 per 100,000 in May 2003) and are not usually deemed serious. In fact, familiarity with symptoms was a key initial obstacle in preventing SARS spread in hospitals (7) and remains an impediment to raising community alertness.

In our sample, anxiety appeared to motivate preventive behavior; those in the highest anxiety group took more precautions. However, anxiety was not associated with the perceived likelihood of contracting SARS. The low percentage of respondents who viewed SARS as a personal risk (14%, compared to 22% found in a similar survey in Toronto [8]) could be explained by the fact that healthcare workers were among the first SARS patients. By the time the interviews began, two physicians had died, and two hospitals had clusters of cases. Lay respondents (those with no contact with hospitals or healthcare workers) may have perceived SARS an occupational hazard.

Distribution of SARS information and prevention advice in Singapore increased rapidly over the 2 months preceding the interviews. All types of media were used, including a public television channel, the "SARS Channel," established to give current and comprehensive information on world infection trends and Singapore's situation. The Ministry of Health provided SARS information on its Web site (9), taking advantage of the fact that, as of December 2001, Singapore had 1.9 million Internet subscribers (out of 3.3 million population) (10). Of respondents, 20.7% were able to correctly answer all three SARS questions, and these did not differ in the practice of preventive measures from those who had less SARS knowledge. The absence of a correlation between knowledge and behavior confirms that knowledge of a disease is not sufficient to trigger preventive action (5,6,11–13).

Since SARS appeared unexpectedly, healthcare experts were uncertain how to control the epidemic. Consequently, assessing public opinion of authorities' crisis management in our survey was relevant to Singapore. Of the aspects we examined, only public opinion of authorities' openness to communication was correlated with taking preventive measures. The other two aspects (information dissemination and acceptance of quarantine regulations) did not affect preventive action, probably because of their very positive rating.

The public's highly positive assessment of Singapore authorities' crisis management is distinctive. History shows that epidemics are politically perilous to governments as, among other things, they challenge their resolve, efficiency, and state of readiness (14). Political leaders of other SARS-affected Asian countries witnessed this principle directly. The SARS outbreak in Singapore appears to have worked in an opposite way: it corroborated the usefulness of public health and environmental regulations. In addition, this study's findings parallel the population's response to quarantine and other restrictive measures, confirming previous observations of a relatively high level of social discipline in the population (15,16).

Conclusion

Singapore was taken out of the official list of SARS-infected countries by the World Health Organization on May 30, 2003. The epidemic has left the crisis phase and entered a new phase, normalization and vigilance. As a new disease, SARS demands continuous scrutiny on all fronts, from the laboratory to the homes of the people.

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SARS Preparedness Checklist for State and Local Health Officials

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A planning checklist for widespread severe acute respiratory syndrome, modeled on an Association of State and Territorial Health Officials (ASTHO) pandemic influenza planning checklist, was developed jointly by ASTHO, the National Association of County and City Health Officials, and the Centers for Disease Control and Prevention. This checklist, distributed May 2003, has been widely used.

In March 2003, the number of cases of severe acute respiratory syndrome (SARS) was increasing daily worldwide, and several cities were having difficulty bringing its transmission under control (1). SARS appeared to have pandemic potential, as all persons worldwide were susceptible and the disease was, under certain conditions, readily spread from person to person. The Centers for Disease Control and Prevention (CDC) developed a multifaceted response to this worldwide and domestic threat, organized in a wide range of investigative and response teams. As part of this response, a team was created and tasked with identifying the types of public health response that would be needed in the United States at various stages if a SARS pandemic occurred, with widespread disease in the United States and with transmission in health care facilities and the community. The team included members with experience in planning for pandemic influenza and for smallpox control, should that disease reappear. Several influenza planning documents had been produced and provided support and encouragement to state and local health departments to develop their own influenza pandemic plans (2).

In examining existing influenza planning documents, the team became aware of a pandemic influenza planning checklist designed for state health officials, which had been produced and disseminated as part of a larger influenza planning guidance document by the Association of State and Territorial Health Officials (ASTHO) (3). This document identified a wide range of topics and issues that would need to be considered at the state level in planning for pandemic influenza, ranging from ensuring adequate legal authority and issuing of emergency declarations to organizing volunteer medical assistance, coordinating healthcare services and emergency provision of vaccine and antiviral medications, communicating with healthcare providers and the public, and providing laboratory and epidemiology services. The team believed that this well-received checklist could, with relatively minor modifications, be adapted for SARS planning, at both the state and local levels, to ensure that important preparedness issues were recognized and addressed by SARS planning teams. The checklist might serve as the outline for a SARS plan or be used in review of an existing or developing plan to ensure that key issues were addressed.

A joint workgroup of ASTHO and the National Association of County and City Health Officials (NACCHO) members and staff and CDC representatives convened by telephone in early April 2003. As a result of a series of conference calls, the checklist was modified to address local and district as well as state health officials' roles; surveillance, epidemiologic investigation, isolation, and quarantine; and transmission in healthcare settings. The material on vaccination and antiviral drug treatment was moved to an appendix.

The revised checklist (Appendix) was reviewed and approved by appropriate committees and managers of ASTHO, NACCHO, and CDC (National Center for Infectious Diseases). It was posted as a joint NACCHO-ASTHO document on the Web sites of both organizations on May 29, 2003 (4). Through electronic newsletters, NACCHO and ASTHO each alerted their members that the document was available. For example, NACCHO emailed approximately 3,000 local health department managers, 1,547 local health department immunization coordinators, and approximately 1,600 local health department bioterrorism coordinators. The checklist was also included in NACCHO's Public Health Dispatch of July 2003, which is distributed by regular mail to all NACCHO members (5). ASTHO distributed the checklist by email to each state health official, other senior public health staff, and affiliate

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organizations on May 30, 2003, and notified approximately 1,200 public health personnel through the print version of the ASTHO Report. During June and July 2003, the checklist was accessed approximately 1,600 times on the NACCHO Web site.

On May 28 and 29, 2003, NACCHO used the checklist as the organizing document for a 2-day working meeting in Chicago, Illinois, of representatives of more than 20 large city health departments, held to develop recommendations for managing possible epidemic SARS in metropolitan areas. The checklist was presented and discussed in a plenary session of the July 9–11 ASTHO meeting of senior deputies in Park City, Utah. The checklist was favorably cited July 29, 2003 by Dr. Marjorie Kanof of the U.S. General Accounting Office in congressional testimony about national readiness for a resurgence of SARS (6).

The checklist has been used by state public health agencies as a guiding document for SARS preparedness planning and has been included as an appendix in some state SARS public health emergency response plans. In addition, the Chicago Department of Health is using the checklist to make plans for dealing with SARS control in its pediatric population through pediatric providers. The Santa Clara (California) County Health Department has used the checklist to work with its hospitals and clinical laboratories in coordinating their SARS plans. The Dallas County Health Department has used it to review legal authority issues and to work with hospitals and law enforcement on isolation and quarantine issues (J. Ransom, unpub. data). As experience accumulates from using the checklist as a framework for local and statewide SARS planning, the document may be revised. As of December 2003, SARS transmission is not known to be occurring anywhere in the world (7). The quick development and widespread acceptance of this checklist suggest that with periodic updating and modification such a planning document can be a useful tool for managing serious infectious disease threats. The value of plans developed using this checklist should be assessed in each community by carrying out realistic table-top and field exercises that involve all partners identified in the plan.

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Appendix. State and Local Health Official Epidemic SARS Checklist

LEGAL AND POLICY ISSUES

- ❑ 1. My jurisdiction has a draft or formally adopted epidemic SARS plan.
- ❑ 2. Agreements have been obtained with my state's healthcare insurers, Medicaid program, and healthcare product and service providers for cooperation with public health recommendations during an epidemic.
- ❑ 3. I have reviewed with legal counsel my jurisdiction's laws and procedures on quarantine, isolation, closing premises, and suspending public meetings and know how to implement them to help control an epidemic.
- ❑ 4. I am familiar with my state's medical volunteer licensure, liability, and compensation laws for in-state, out-of-state, returning retired, and nonmedical volunteers.
- ❑ 5. I know whether my state allows hospitals and other licensed healthcare institutions to use temporary facilities for provision of medical care in the event of a public health emergency.
- ❑ 6. My jurisdiction's epidemic plan addresses Worker's Compensation and Unemployment Compensation issues related to healthcare and other workers missing work because of isolation or quarantine.
- ❑ 7. I have identified any deficiencies in my jurisdiction's laws and procedures on quarantine, isolation, and related capacities and initiated steps to have those deficiencies corrected.
- ❑ 8. I know what provisions are in place, if any, for compensation of persons with economic or health injury resulting from needed SARS control measures and for limitation of liability of healthcare providers and agencies.

AUTHORITY

- ❑ 9. My state has an executive SARS epidemic planning committee that oversees the planning process, in cooperation with local health agencies.
- ❑ 10. My state has identified the authority responsible for declaration of a public health emergency and for officially activating our plan during a SARS epidemic.
- ❑ 11. My jurisdiction has identified key stakeholders responsible for development and implementation of specific components of the SARS epidemic plan, including enforcement of isolation, quarantine, and closure and decontamination of premises.
- ❑ 12. My jurisdiction's elected officials, appointed officials, and other agency heads know their respective responsibilities in the event of an epidemic.
- ❑ 13. My jurisdiction has a command system in place (e.g., the Incident Command System) to govern roles and responsibilities during a multiagency, multijurisdictional event.

- ❑ 14. I am familiar with the controlling authority over intrastate and interstate modes of transportation, should these need to be curtailed during an epidemic (e.g., airplanes, trains, ships, highways).
- ❑ 15. My staff has relationships with health authorities of adjoining counties or states and with federal agencies to ensure effective communication during a public health emergency.
- ❑ 16. My jurisdiction has identified an overall authority in charge of coordinating different medical personnel groups during an epidemic.
- ❑ 17. I know personally the key persons from the state and local authorities who will assist in maintaining public order and enforcing control measures, if needed, during an epidemic.
- ❑ 18. I am familiar with the procedure for enlisting the National Guard's assistance during a public health emergency.

SURGE CAPACITY

- ❑ 19. I know how to access current recommendations on treatment of cases and prevention of transmission in the hospital, long-term, care and home care settings.
- ❑ 20. My jurisdiction's emergency response planning has involved healthcare product and service providers to determine how to best prevent and control disease spread and manage the healthcare of the population during an epidemic.
- ❑ 21. I am familiar with the required protocol for securing needed emergency healthcare services and supplies during a public health emergency.
- ❑ 22. My jurisdiction has identified ways to augment medical, nursing, and other healthcare staffing to maintain appropriate standards of care during an epidemic.
- ❑ 23. My jurisdiction has identified ways to augment public health laboratory, epidemiology, and disease control staffing to meet emergency needs and in the event public health workers are affected by an epidemic.
- ❑ 24. My jurisdiction has a process to recruit and train medical volunteers for provision of care and vaccine administration during a public health emergency.
- ❑ 25. My jurisdiction has identified alternate facilities where overflow cases from hospitals and well persons needing quarantine away from home can be cared for and has developed processes with Emergency Medical Services to assess, communicate, and direct patients to available beds.
- ❑ 26. My jurisdiction has identified facilities for outpatient and inpatient care of children with SARS and their families.
- ❑ 27. My jurisdiction's epidemic plan addresses the mechanics of how isolation and quarantine will be carried out, such as providing support services for people who are isolated or quarantined to their homes or temporary infirmary facilities and protection for workers providing these services.
- ❑ 28. My jurisdiction has a plan for ensuring that appropriate personal protective equipment, including N-95 or higher level respirators, is made available for persons whose job requires exposure to people with SARS, and that needed training and fit-testing are provided.
- ❑ 29. My jurisdiction has a plan for dealing with mass mortality, including transportation and burial of bodies.
- ❑ 30. My jurisdiction has a plan for providing mental health services to mitigate the impact of a SARS epidemic.

COMMUNICATIONS AND EDUCATION

- ❑ 31. I have conveyed the importance of epidemic preparedness, and its overlap with bioterrorism preparedness, to my jurisdiction's chief executive and to other state and local law and policy makers.
- ❑ 32. I know personally the key persons from public health agencies, the medical community, and the political community with whom I will need to communicate during an epidemic.
- ❑ 33. My jurisdiction has begun educating the public on epidemic SARS to instill acceptance of the epidemic response (including quarantine and isolation) and to optimize public assistance during an epidemic.
- ❑ 34. My jurisdiction has opened a regular channel of communication and begun educating healthcare providers (including first responders) and their organizations and unions on epidemic SARS (including diagnosis, treatment, and management of cases and contacts to prevent transmission).
- ❑ 35. My jurisdiction has opened a regular channel of communication and begun educating chief executive officers of healthcare organizations on epidemic SARS (including management of patients in healthcare settings, healt care worker protection, physical facility needs, voluntary or forced furloughs of exposed workers, etc.).
- ❑ 36. My jurisdiction has established a multicomponent communications network and plan for sharing of timely and accurate information among public health and other officials, medical providers, first responders, the media, and the general public.
- ❑ 37. My jurisdiction has begun identifying and planning to produce and provide education and information materials for media, providers, the public, and occupational groups whose duties may expose them to SARS, in appropriate languages and in forms suitable for limited literacy populations.
- ❑ 38. Whoever is selected as the primary public spokesperson for my jurisdiction during an epidemic is ready to clearly and consistently answer the following types of questions:

  How is the SARS-associated coronavirus (SARS-CoV) transmitted?
  How long are people infectious after they have SARS?
  What is isolation? What is quarantine?
  What is the justification for isolation of cases and quarantine of contacts?
  What is the legal authority for isolation of cases and quarantine of contacts?
  What is the difference between a probable and a suspected SARS case?
  Who should be tested for SARS-CoV?
  What can members of the public do to protect themselves?
  In the event a vaccine or antiviral treatment become available, what specific priority groups might be vaccinated or treated first?

- ❑ 39. My jurisdiction has identified the most effective media to get messages out to the public during an epidemic (e.g., TV, radio, print media, internet, Web sites, hotlines).
- ❑ 40. My jurisdiction has planned how to coordinate state, local, and federal public messages and ensure they are consistent and timely.

LABORATORY AND SURVEILLANCE

- ❑ 41. In the event of a SARS epidemic, I will have available daily counts of key community health indicators, such as numbers of emergency department visits, hospital admissions, deaths, available hospital beds and staff, facility closings, numbers of contacts being traced, and numbers under quarantine.
- ❑ 42. The public health laboratory that serves my jurisdiction can test for SARS-CoV by serology, polymerase chain reaction, or both.
- ❑ 43. My state has identified those laboratories that can test for SARS-CoV.
- ❑ 44. The public health laboratory that serves my jurisdiction has linked to clinical laboratories and provided training on the use of SARS tests, biosafety, specimen collection, packing and shipping, and rule-out testing.
- ❑ 45. Public health laboratories in my state have computerized record-keeping to help with data transmission, tracking, reporting of results to patients and facilities, and analysis during an epidemic.
- ❑ 46. My jurisdiction has determined how to assess and document the spread and impact of disease throughout the population, including special populations at risk (such as healthcare workers and first responders), during a SARS epidemic, including enhancements to routine surveillance.
- ❑ 47. My jurisdiction has computerized record-keeping for cases, suspected cases, contacts, and persons under public health isolation or quarantine orders to help with data transmission, tracking, and analysis during an epidemic.
- ❑ 48. My jurisdiction's epidemiology staff, in cooperation with other public health agencies, has the capacity to investigate clusters of SARS cases determine how disease is being transmitted trace and monitor contacts implement and monitor quarantine measures determine whether control measures are working.
- ❑ 49. My jurisdiction has plans for educating healthcare providers about recognition and reporting of SARS, about the current case definition, and about sources of current information on all aspects of SARS.

PREPAREDNESS IN OTHER AGENCIES

- ❑ 50. The emergency response system is ready to deal with epidemic SARS, as called for in an all-hazards or epidemic plan.
- ❑ 51. My jurisdiction has carried out a community-wide epidemic SARS table-top or field exercise, to train on and evaluate its epidemic plan.
- ❑ 52. Community partners such as hospitals, EMS services, law enforcement agencies, healthcare practitioners, environmental hygiene/remediation services, news media, schools, and colleges know what part they are expected to play during an epidemic and are prepared to do so.
- ❑ 53. The law enforcement and court system in this jurisdiction are prepared to enforce isolation and quarantine orders and to promptly adjudicate appeals to public health orders, as provided by statute.

Use of trade names is for identification only and does not imply endorsement by the Public Health Service or by the U.S. Department of Health and Human Services.

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Body Temperature Monitoring and SARS Fever Hotline, Taiwan

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In Taiwan, a temperature-monitoring campaign and hotline for severe acute respiratory syndrome (SARS) fever were implemented in June 2003. Among 1,966 calls, fever was recorded in 19% (n = 378); 18 persons at high risk for SARS were identified. In a cross-sectional telephone survey, 95% (n = 1,060) of households knew about the campaign and 7 households reported fever.

Fever is one of the first signs of severe acute respiratory syndrome (SARS) (1–3). Persons with fevers initially attributed to other illnesses have caused outbreaks of SARS in hospitals and the community (1–7). This finding highlights the need for early recognition of cases.

On June 1, 2003, in Taiwan, a National Temperature Monitoring Campaign and SARS fever hotline were launched. These were intended to raise public awareness about SARS (and fever as an early sign of SARS), improve early detection of possible SARS cases, and prevent SARS transmission. In the campaign, fever was defined as forehead or axillary temperature >37°C, oral temperature >37.5°C, or tympanic or rectal temperature >38°C (8).[2]

In conjunction with this campaign, persons with fevers were encouraged to call a toll-free SARS fever hotline. The hotline objectives were to appropriately triage persons with fever, reduce clinic visits by the "worried well," identify persons at high risk for SARS, reduce opportunities for SARS exposure, and increase the public's sense of security.

Both the body-temperature monitoring campaign and the hotline were publicized through television, posters, fliers, radio, the Internet, magazines, and newspapers. We describe and evaluate the body-temperature monitoring campaign and the SARS fever hotline.

Methods

Our investigation evaluated the community-wide body-temperature monitoring campaign and SARS fever hotline in the city of Taipei, which makes up 11.8% of the population of Taiwan (population of Taiwan, 22.51 million [9]). We analyzed data from three sources: hotline call data reported to the Bureau of National Health Insurance for all of Taiwan; hotline call data for Taipei; and data from a telephone survey of Taipei residents. Data were evaluated for the period June 1–10, 2003, corresponding to the duration of the body-temperature monitoring campaign as well as the first 10 days of the hotline.[2]

SARS Fever Hotline Data

Throughout Taiwan, each local medical association responsible for operating the fever hotline in its city or county provided daily reports to the Bureau of National Health Insurance. The total number of calls and the advice given to the caller were reported. Because operation of the hotline varied by locality, further analysis was limited to Taipei city, where the Taipei Medical Association staffed the hotline and 52 physicians worked 6-hour shifts between 8:00 a.m. and 10:00 p.m. daily. Physicians were provided with an algorithm (Figure 1) for triaging callers and evaluating SARS risk level. Persons at high risk for

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[2]See also additional text and visuals in online version.

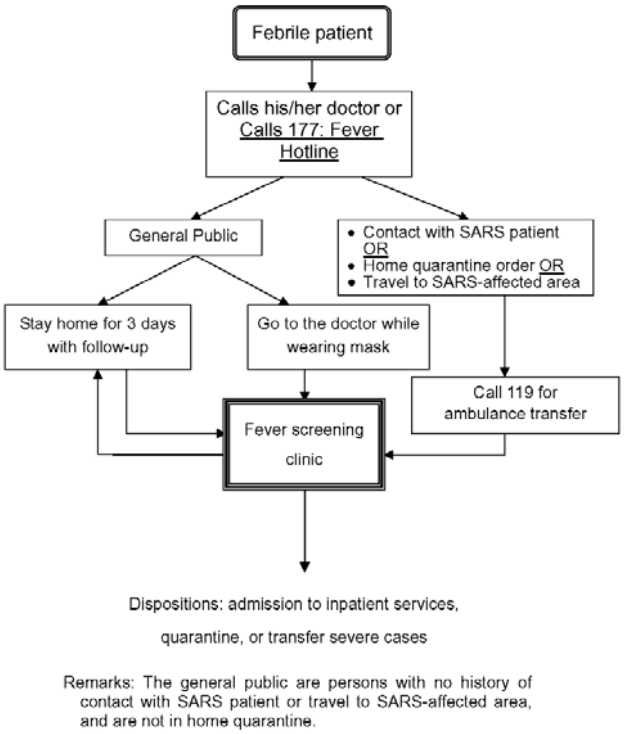

Figure 1. Triage algorithm for febrile patients, severe acute respiratory syndrome fever hotline, Taipei, June 2003.

SARS were defined as those with fever plus any recent history of quarantine, travel to SARS-affected areas, or contact with SARS cases. Physicians also received a form to document all calls. Data fields on the form were caller or patient name, sex, district of residence, telephone number, a section for comments, a checklist of topics discussed, and diagnosis. The diagnosis field was narrative; therefore, data were classified into broad categories based on the body part or system affected. The hotline data collection forms did not include anatomic site of temperature measurement, therefore, for our evaluation, fever was defined as a recorded body temperature of ≥38°C.[2]

Cross-Sectional Telephone Survey of Taipei Residents

A telephone survey of Taipei city residents was performed to assess knowledge of the body-temperature monitoring campaign and use of the fever hotline. Households in Taipei were selected for participation in the survey on June 13 to 14, 2003, using a simple random sample of home telephone numbers. Interviewers explained the survey to potential respondents and obtained verbal consent before administering a brief questionnaire.

The Yates corrected chi-square test and the Fisher exact test were used for comparison of groups.

Results

Taiwan SARS Fever Hotline Data

During June 1 to 10, a total of 11,228 calls were made to Taiwan's population-wide fever hotline (Figure 2). Persons were advised to seek further medical evaluation (through family physician, fever clinic, or by ambulance) in 28% (n = 3,100) of calls, and persons were advised to remain at their residence and monitor symptoms in 21% (n = 2,385) of calls. Neither of these recommendations was given in 51% (n = 5,743) of calls.

Taipei SARS Fever Hotline Data

During June 1 to 10, a total of 1,966 calls were made to the fever hotline in Taipei. Body temperature was recorded for 51% (n = 1,012) of calls. A temperature of ≥38°C (range 34.0°C–41.0°C, median 37.6°C) was recorded in 37% (n = 378) of calls in which body temperature was recorded. Of the 453 calls with diagnoses, the most common were respiratory and gastrointestinal syndromes (Table 1) for persons with or without fevers. Among calls for which the recommendation given was documented, callers with fever were more likely than callers without fever to be advised to see a physician for further medical evaluation ($p < 0.001$) or go to a fever clinic ($p < 0.001$) (Table 2).

Eighteen (0.9%) persons were identified as being at high risk for SARS. Of these, 5 (28%) had fever, 2 (11%) had no fever, and temperature was unrecorded for 11 (61%). One person with unrecorded temperature was advised to stay home and monitor symptoms, and one person with a fever was advised to visit a physician. The advice given to the remaining 16 persons was not recorded.

Cross-Sectional Telephone Survey of Taipei Residents

Of the 4,000 telephone numbers dialed, 2,999 numbers were invalid, unanswered, or refusals. Of the 1,111 survey participants, 58% (n = 643) were female, the median age was 47 years (range 20–91), and the median number of people per household was 4 (range 1–17). Ninety-five

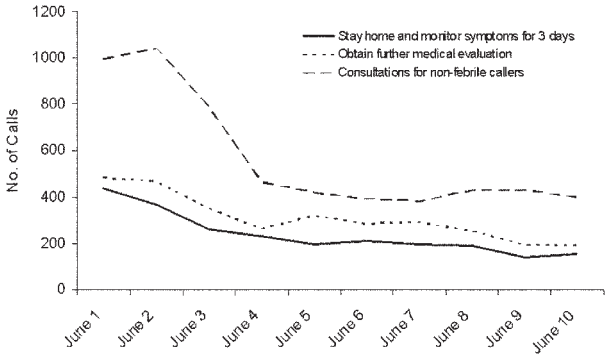

Figure 2. Advice given to callers to severe acute respiratory syndrome fever hotline, Taiwan, June 2003.

Table 1. Diagnoses reported for callers by recorded body temperature, Taipei SARS fever hotline, June 1–10, 2003 (n = 1,966)[a]

	Body temperature		
Diagnosis or syndrome	Fever ≥38°C (%)	No fever (%)	Unknown/unrecorded
Possible SARS	5 (1.3)	2 (0.3)	11 (1.2)
Respiratory	65 (17.2)	99 (15.6)	40 (4.2)
Dermatologic	0 (0)	1 (0.2)	3 (0.3)
Head-related[b]	6 (1.6)	10 (1.6)	2 (0.2)
Gastrointestinal	21 (5.6)	47 (7.4)	14 (1.5)
Genitourinary	7 (1.9)	8 (1.3)	4 (0.4)
Other	27 (7.1)	31 (4.9)	50 (5.2)
Unknown/missing	247 (65.3)	436 (68.8)	830 (87.0)
Total	378	634	954

[a]SARS, severe acute respiratory syndrome.
[b]Includes neurologic.

percent (n = 1,060) and 71% (n = 791) of respondents had heard about the body-temperature monitoring campaign and the fever hotline, respectively. The most common sources of information about the campaign were television (86%), newspapers or magazines (36%), and neighborhood leaders (26%). Twice-daily temperature monitoring of at least one household member was reported by 95% (n = 1,012) of persons who knew of the campaign and 76% of the 51 who were unaware of the campaign (n = 39).

Seven (0.63%) respondents reported a fever in their household during June 1 to 10, 2003. Although five (71%) of these fevers occurred in households in which the respondent knew about the hotline, in only one case was the fever hotline used; actions of the remaining six are unknown. The person who called the hotline reported that the advice given by the physician was to stay home and monitor the symptoms and that the advice was followed. Among all respondents, 24% (n = 267) said that they would call the fever hotline for advice, 54% (n = 605) would go to a hospital, 19% (n = 207) would visit an outpatient clinic, and 1% (n = 10) would do nothing and wait to see if the fever disappeared. The remaining respondents refused or said they would do something else.

Discussion

The population-wide body-temperature monitoring campaign and fever hotline were innovative interventions aimed at raising public awareness about SARS, improving early detection of fever, and providing appropriate medical triage. Developed as an emergent response to the SARS outbreak in Taiwan, these interventions were rapidly implemented, leaving little time available to develop hotline data-collection instruments, train hotline staff, or prospectively plan for intervention evaluation. Despite these challenges, the interventions were evaluated by using available data, and a rapidly implemented population-based survey of Taipei city residents.

Approximately 50% of calls to the population-wide fever hotline did not result in referrals for further evaluation of fever, suggesting they were complaints unrelated to fever. In Taipei, 37% of respondents with body temperature recorded had fevers, a low proportion for a hotline intended for persons with fever. The low proportion of febrile persons is likely partly due to the definition of fever used in this evaluation. These results might also be partially due to worried-well callers. To improve appropriate use of a dedicated SARS fever hotline, media messages should be refined and the use of alternative resources for answering more general questions about SARS should be encouraged. During the outbreak, the Center for Disease Control of Taiwan established a public information line about SARS. If a fever hotline is used in future outbreaks, callers could be referred to the public information line with questions about temperature measurement, travel concerns, and other issues not directly related to a current febrile illness. The dedicated hotline

Table 2. Reported advice given to persons by recorded body temperatures, Taipei SARS fever hotline, June 1–10, 2003 (n = 1,966)[a]

	Body temperature		
Advice given	Fever ≥38°C (%)	No fever (%)	Unknown/unrecorded (%)
Stay home and monitor[b]	19 (5.0)	42 (6.6)	21 (2.2)
See physician[b]	116 (30.7)	55 (8.7)	40 (4.2)
Go to fever clinic	21 (5.6)	2 (0.3)	5 (0.5)
Call ambulance	1 (0.3)	0 (0)	0 (0)
Unknown or unrecorded[b]	221 (58.5)	535 (84.4)	888 (93.1)
Total	378	634	954

[a]SARS, severe acute respiratory syndrome.
[b]Advice given to 18 callers at high risk for SARS: for 5 with fever: see physician (1 caller); unknown or unrecorded (4 callers). For 2 callers with no fever: unknown or unrecorded (2 callers). For 11 callers with unknown body temperature: stay home and monitor (1 caller); unknown or unrecorded (10 callers).

could then focus on addressing its stated objectives more efficiently.

In the population-based survey, almost all respondents knew about the body-temperature monitoring campaign, and 71% knew about the fever hotline. The Bureau of National Health Insurance was highly successful in publicizing the campaign and hotline and should consider using similar methods for future hotlines.

An important aspect of this evaluation is assessing the potential impact of these interventions on improving early SARS detection. Eighteen callers to the fever hotline were identified as being at high risk for SARS. Because these persons were not followed up for outcome, determining if any subsequently met the World Health Organization's suspected or probable SARS case definition was not possible. Furthermore, because hotline data were not always collected systematically, determining if all callers at high risk for SARS were identified was difficult. Lastly, sparse risk factor data limit our ability to determine if more persons at high risk for SARS should have been identified. Taking these limitations into account, the hotline potentially identified an estimated cohort of persons at high risk for SARS equivalent to 9.5% of the 190 suspected and probable SARS cases reported in Taiwan in the same 10-day period.

Documentation of the advice and referrals given by physicians was missing for a substantial proportion of calls; therefore, judging whether these callers were appropriately referred is not possible. The reasons for missing data are not yet fully elucidated. A telephone survey of callers to the Taipei SARS fever hotline is in progress to assess advice and referrals given and caller compliance. An algorithm and accompanying questionnaire that includes clearly articulated steps to measure temperature and document risk factors might assist in standardizing risk assessment, advice, referrals, and evaluation in future outbreaks.[2]

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Health Communication during SARS

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During the severe acute respiratory syndrome (SARS) outbreak, electronic media made it possible to disseminate prevention messages rapidly. The Centers for Disease Control and Prevention's Travelers' Health Web site was frequently visited in the first half of 2003; more than 2.6 million visits were made to travel alerts, advisories, and other SARS-related documents.

Experience with the outbreak of severe acute respiratory syndrome (SARS) has reinforced the importance of a multipronged approach to preventing disease transmission. Timely health communication, along with surveillance, quarantine, isolation, and travel restrictions, figured prominently among the tools the Centers for Disease Control and Prevention (CDC) used to help contain the outbreak. During the SARS response, health communication was shown to be an integral element by ensuring that knowledge about prevention measures reached the public, healthcare providers, the media, and other stakeholders.

Disseminating information and educational materials is a key element of CDC's response to disease outbreaks that affect international travelers. Electronic media greatly expedite the process of dissemination and enable prevention messages to reach an expanded audience. The SARS response may be compared with a situation approximately 10 years before, when an outbreak of plague occurred in India (1). In both situations, the challenge was to control a disease outbreak that had potential for rapid international spread and to provide guidance tailored for specific audiences.

Plague Outbreak, 1994

In late August 1994, CDC received reports from India of an epidemic of plague, the first such outbreak in 24 years. Within 2 months, 5,150 cases of either bubonic or pneumonic plague were reported to the World Health Organization from eight Indian states (2). Fifty-six deaths were reported, and >100,000 people fled Surat, a city of approximately 2 million. Neighboring nations closed their borders to travelers and cargo from India, and flights were discontinued.

CDC recognized the need for rapid dissemination of comprehensive educational materials to ameliorate the panic. By the end of September 1994, CDC had produced six documents to distribute to public health officials: an outbreak notice; a plague advisory for travelers to India; a plague alert notice handed to passengers arriving from India, which described the symptoms of plague and urged them to seek medical attention if they developed a febrile illness within 7 days; recommendations for treatment and prophylaxis; guidelines for diagnosis and biosafety; and a review article in the Morbidity and Mortality Weekly Report. These documents were disseminated through an automated fax information service, a voice information service, and a telephone hotline, as well as traditional print media. The fax service reported that 5,589 documents were requested regarding the plague outbreak.

Because of the high volume of air travel from India (approximately 2,000 arriving passengers daily at John F. Kennedy International Airport on flights from India), the departments of health in New York City and New York State supplemented CDC's surveillance plan by using two approaches to disseminate information to heighten awareness of plague, focusing on emergency department physicians. First, a fact sheet was transmitted by fax or electronic mail to emergency department physicians and infection-control practitioners at 102 hospitals in New York City and to all acute-care hospitals and county health departments in the state. Second, a special plague advisory was distributed to 20,000 physicians in New York City (3).

SARS Response, 2003

The need for educational materials to heighten the awareness of healthcare providers and the public about SARS became obvious early in the outbreak. Because information was rapidly evolving, guidelines needed to be flexible. The "interim" document, one that required constant updating, became the norm. The Internet became a primary tool for communication, as it has been for CDC

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travelers' health information. In fact, before the SARS outbreak, the travelers' health Web site (located within the CDC Web site; available from: URL: www.cdc.gov/travel) had become the most frequently visited CDC Web site other than the home pages, with more than 3.6 million visits recorded in 2002 (Figure 1). Visits to the Web site increased dramatically in 2003. As of July, >4 million visits had been recorded to the travelers' health Web site; more than 1 million of these visits resulted from accessing SARS-related content (travel alerts and advisories). Although the target audience for this Web site is in the United States, approximately one third of the visits were from other countries. In May, the city from which the most visits originated was Taipei, Taiwan, with more visits than any city in the United States. The SARS-related documents were not posted in multiple areas on the Web site but could be accessed by navigating through the Web site using different routes. Data from Web-tracking software showed that approximately 83% of visitors came from a commercial or .net domain, 10% from educational domains, 3% from .org domains, 2% from government domains, and 1.5% from military domains.

As part of the SARS response, CDC's Division of Global Migration and Quarantine (DGMQ) developed travel-related information and recommendations, as well as industry-specific guidelines. Web sites that referred to these pages with a substantial number of visits included those from 1) organizations serving constituent groups such as families adopting children from Asia and expatriates overseas, 2) organizations with major meetings or conferences in areas with SARS, and 3) major news organizations. Overall, during the outbreak, DGMQ generated >125 documents, including updates and translations into seven languages, which were posted on the SARS pages of the CDC Web site. This material was written for multiple audiences, from highly technical to low literacy, and was disseminated through multiple platforms, from traditional print (e.g., >2,700,000 yellow Health Alert Notices were handed out by Quarantine Officers to passengers disembarking from 11,840 flights from areas with SARS) to electronic (postings on Web sites and CDC's Secure Data Network).

As the outbreak matured and additional stakeholders were identified, interim guidelines were tailored to the specific concerns of healthcare providers, industry, and the traveling public (Table). Fact sheets explaining the legal authority for isolation and quarantine were written and posted. More than 1.5 million visits were made to DGMQ documents on CDC's SARS Web site, in addition to the 4 million visits to the Travelers' Health Web site.

The travel alerts and advisories received the most visits (Figure 2). Historically, CDC has never advised against travel to any region, even during the plague epidemic in India. However, because of the rapid spread of SARS, its short incubation period, and the potential severity of illness, the need was recognized to codify different levels of concern about potential transmission to travelers. Thus, the travel alert and advisory system was developed.[1]

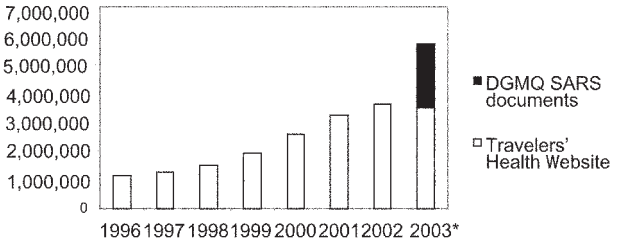

Figure 1. Visits to Centers for Disease Control and Prevention's (CDC) Travelers' Health Web site, 1996 through July 2003. * 2003 = Jan–July only, includes documents posted on the CDC SARS Web site as well as the Travelers' Health website.

A travel alert is a notification by CDC that an outbreak of a disease is occurring in a geographic area. Its purpose is to provide information to travelers and resident expatriates about the status of an outbreak, how to reduce their risk for infection, and what to do if they become ill. The risk for individual travelers is thought to be definable and limited. In contrast, a travel advisory recommends against nonessential travel to an area because the risk to travelers is considered to be high as a result of ongoing transmission or inadequate containment. The travel advisory not only provides information about the status of an outbreak, but also is intended to reduce risk for exposure by decreasing the volume of traffic to the affected area.

These designations were used for the first time during the SARS outbreak, and thus criteria for their introduction, downgrading, and removal were required. Institution of either an alert or advisory was dependent on the magnitude and scope of the outbreak, the containment measures being used, the quality of surveillance in the affected area, and the quality and accessibility of medical care, all of which are based on reports from the involved countries. Once instituted, downgrading an advisory to an alert required adequate surveillance and no evidence of ongoing transmission for at least two incubation periods after the date of onset of symptoms in the last case (for SARS, 20 days). Removing an alert was dependent on the above criteria, as well as lack of evidence of new cases for three incubation periods (for SARS, 30 days) and no exportation of cases, as determined by an assessment of the information reported from the countries involved.[2]

[1]In the 1994 plague documents, the term "advisory" did not have the same connotation.

[2]These criteria differed from those used by the World Health Organization.

Table. SARS-related documents generated by the Division of Global Migration and Quarantine, Centers for Disease Control and Prevention, March–July 2003[a]

Category	Document	Mo. of initial version	URL
Travelers/Public	Interim travel advisories and alerts	March	http://www.cdc.gov/travel/
	Health Alert Notice (in 7 languages)	March	http://www.cdc.gov/ncidod/sars/travel_alert.htm
	Interim definitions and criteria: travel alerts vs. travel advisories	May	http://www.cdc.gov/ncidod/sars/travel_alertadvisory.htm
	Interim guidelines about SARS for persons traveling to areas with SARS	April	http://www.cdc.gov/ncidod/sars/travel_advice.htm
Legal and Quarantine	Fact sheet: isolation and quarantine	April	http://www.cdc.gov/ncidod/sars/isolationquarantine.htm
	The SARS investigation: the role of CDC's division of global migration and quarantine	March	http://www.cdc.gov/ncidod/sars/roleofdq.htm
	Questions & answers: travel and quarantine	April	http://www.cdc.gov/ncidod/sars/qa/travel.htm
	Fact sheet on legal authorities for isolation/quarantine	April	http://www.cdc.gov/ncidod/sars/factsheetlegal.htm
Industry Specific Guidelines	Interim guidelines about severe acute respiratory syndrome (SARS) for airline flight crew members	March	http://www.cdc.gov/ncidod/sars/flight_crew_guidelines.htm
	Interim guidelines for cleaning of commercial passenger aircraft following a flight with a passenger with suspected SARS	March	http://www.cdc.gov/ncidod/sars/aircraftcleanup.htm
	Interim guidelines for personnel interacting with passengers arriving from areas with SARS	March	http://www.cdc.gov/ncidod/sars/tsa-bcbp-guidelines.htm
	Interim guidelines about SARS for cruise ship passengers and crew members	April	http://www.cdc.gov/ncidod/sars/cruiseship.htm
	Interim guidelines for personnel boarding maritime vessels from areas with SARS	May	http://www.cdc.gov/ncidod/sars/maritime.htm
	Interim guidelines about SARS for workers handling cargo or other packages	May	http://www.cdc.gov/ncidod/sars/cargoworkers.htm
	Interim guidelines and recommendations: prevention, identification, and management of suspect and probable cases of severe acute respiratory syndrome on cruise ships	May	http://www.cdc.gov/ncidod/sars/cruiseshipguidelines.htm
Other	Interim guidance for institutions or organizations hosting persons arriving in the United States from areas with severe acute respiratory syndrome (SARS)	May	http://www.cdc.gov/ncidod/sars/hostingarrivals.htm
	Interim guidelines for businesses and other organizations with employees returning to the United States from areas with SARS	May	http://www.cdc.gov/ncidod/sars/business_guidelines.htm
	Interim guidelines about SARS for international adoptees and their families	March	http://www.cdc.gov/ncidod/sars/adoption.htm
	Guidance about SARS for Americans living abroad	March	http://www.cdc.gov/ncidod/sars/warden_notice.htm
	Interim guidance: air medical transport for severe acute respiratory syndrome (SARS) patients	March	http://www.cdc.gov/ncidod/sars/airtransport-sarspatients.htm

[a]Documents were updated and revised multiple times.

During the outbreak, the relationship between DGMQ and the airline industry through the Airline Transport Association (ATA) and the airline medical directors was strengthened. As international spread of SARS through airline travel became a possibility, ATA was not only eager to provide information necessary for tracking passengers, but also served as a sounding board for specific guidelines for the traveler, flight crew, cargo handlers, and cleaning crew, and for the management of ill passengers. Other stakeholders included the cruise ship industry and U.S. citizens living overseas.

Conclusions

A comparison of the efforts in mass communication during the Indian plague outbreak that occurred in 1994 with those during SARS is illustrative of the changes that have resulted from the large increase in numbers of travelers, the decreased time in transiting the globe, and the massive demand for instant information (4). Electronic communications media enabled information to reach much wider audiences than had been possible through means such as traditional print media and fax services and allowed distribution of guidelines directed at specific target audiences. During the 1994 plague outbreak, thousands

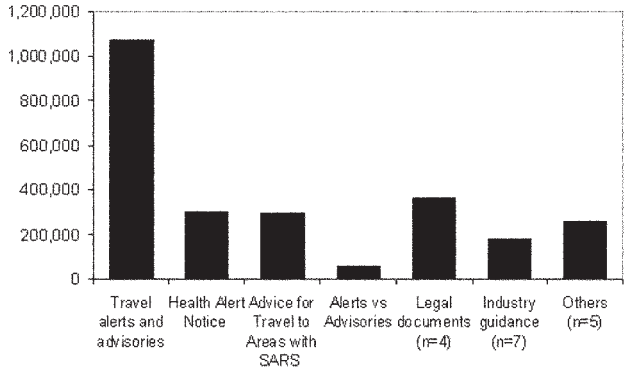

Figure 2. Visits to SARS-related documents posted by Division of Global Migration and Quarantine on Centers for Disease Control and Prevention Web site, January–July 2003.

of documents were distributed by traditional means; during the SARS response, which lasted approximately the same time, millions of documents were disseminated through the CDC Web site.

The opinions expressed by authors contributing to this journal do not necessarily reflect the opinions of the Centers for Disease Control and Prevention or the institutions with which the authors are affiliated.

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SARS Epidemic in the Press

To the Editor: On March 12 2003, the World Health Organization (WHO) issued a global alert regarding severe acute respiratory syndrome (SARS) in Vietnam, Hong Kong, and China's Guangdong Province. Three days later, for the first time in its history, WHO recommended postponing nonessential travel to the affected areas and screening airline passengers (1). These initiatives, together with the awareness of the modes transmission of the coronavirus associated with SARS (SARS-CoV), led to extensive press coverage.

To describe the extent of this coverage in Italy and to identify the events that prompted peak coverage, we reviewed the five Italian daily newspapers with the highest circulation (2) from March 12 to March 30. The articles were identified by hand search (reading headlines, subheads, and titles) and were classified according to the publication date and page number. We assigned one point to full articles and to front-page articles or headlines and half a point to short articles. We also reviewed all national newspapers for articles published before the travel advisory (March 12–15)(Figure).

Before the travel advisory, no articles were published in the five newspapers, whereas on March 14, one article was published in a smaller newspaper ("Osservatore Romano," the Vatican newspaper). On March 16 (the day after the advisory), six articles appeared in the five newspapers; through May 31, a total of 750 articles were published. The proportion of articles that appeared on the front-page was 9.6%, although this percentage was higher early in the study (50%) than at the time of absolute peak coverage (12%).

After the first wave of articles in mid-March, several peaks occurred until mid-April. The events prompting these peaks were identified by determining the most frequently covered topics, specifically: the death of Carlo Urbani, the Italian WHO officer who identified the disease in Hanoi; the first two probable cases in Italy; the death of a suspected case in Naples; and the press conference announcing the first meeting of the Italian National Task Force. The highest peak occurred on April 23, after the announcement that the number of cases had reached 4,000 and that a vaccine would not be available anytime soon. In the days after the peak, coverage remained quite high, in association with the definition of SARS as a "global threat" by WHO and the twofold increase in the number of probable cases in Italy. The high press coverage was followed by an overall decrease, although small peaks occurred in association with the conflicts among European Ministries on airport measures, increased quarantine measures in China, and the identification of the civet cat as a probable source of SARS-CoV. Coverage tended to be greater on weekends, probably because political stories constitute less competition for space on these days.

Evidently, the daily newspaper coverage of SARS has been quite extensive in Italy, especially in the aftermath of WHO alerts and statements by the Ministry of Health regarding new cases and more stringent control measures. During outbreaks of infections, both the media and the public are often criticized for overreacting, yet public concern over serious health hazards is essential in guiding prevention activities (3–5) and in deciding whether to adopt measures that could place restrictions on civil rights, such as quarantine (6). Although we did not evaluate the

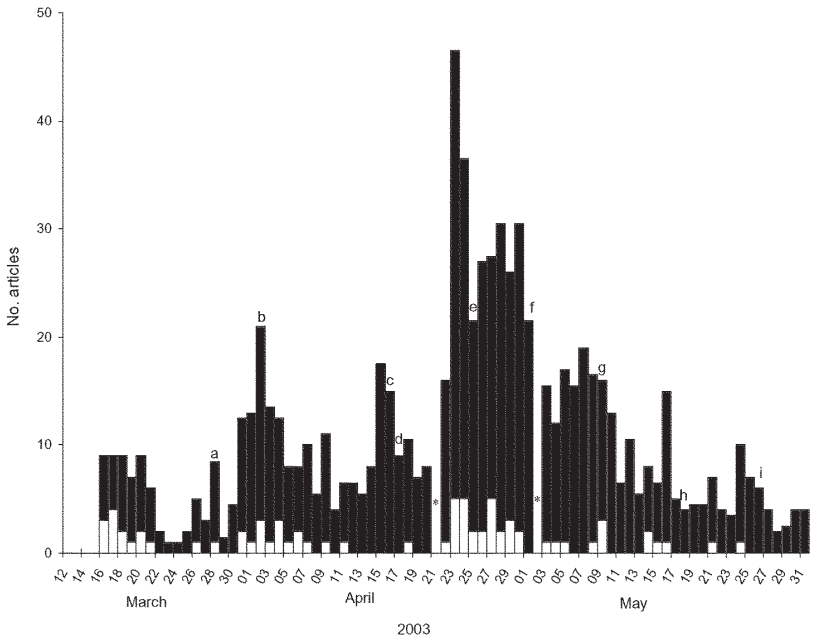

Figure. Number of articles on SARS published in the five newspapers with the highest nationwide circulation in Italy, by date of publication; March 15 to May 31, 2003. The white area of the bars represents the number of articles or headlines appearing on the front page. An asterisk indicates days on which newspapers were not published (Easter and May 1). The World Health Organization (WHO) global alert was March 12 and the WHO travel advisory was March 15. a, death of Carlo Urbani; b, first 2 probable cases in Italy; c, task force press conference; d, death of suspected case in Naples; e, WHO warning of "global threat"; f, two-fold increase of probable cases in Italy; g, European conflict on airport measures; h, increased quarantine measures in China; i, Civet cat identified as probable source.

quality of risk-communication of the journalists or of the experts quoted in the articles, wide press coverage of the WHO global alert may have contributed to public-health bodies' taking action towards containing the epidemic.

Acknowledgments

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SARS-associated Coronavirus Infection in Teenagers

To the Editor: A global outbreak of severe acute respiratory syndrome (SARS) was reported in March 2003 (1). Most reported cases were in adults. Hong Kong, however, reported 10 pediatric cases (2) with less aggressive clinical courses.

The disease became endemic in Taiwan by the end of April 2003 (3). Hualien City, a geographically secluded city in eastern Taiwan, had nine pediatric cases, all mild. The cases occurred in Tzu-Chi High School, a private boarding school for 830 students 12 to 18 years of age, all of whom live in the same building and eat daily meals together in the school cafeteria. On April 28, when a student (case-patient 1) visited the school nurse on the first day that he had a fever, an infection specialist from affiliated Tzu-Chi Medical Center immediately responded. The specialist discovered that this student's close friend in the same class (case-patient 2) was already febrile. Case-patient 2, a Hong Kong resident who leaves Taiwan for Hong Kong every 3 months, had visited Hong Kong twice in March and April 2003. Both students were isolated in the hospital on April 28.

Tzu-Chi Medical Center began a search for other febrile students. On April 29, seven more schoolmates were found to have fever >38°C. All were identified on their first day of becoming febrile and were immediately isolated in the hospital. All nine schoolmates underwent chest x-ray examinations and were tested for SARS-associated coronavirus (SARS -CoV) by reverse transcription–polymerase chain reaction (RT-PCR) (4) and DNA sequencing. The tested length for SARS-CoV was 340 bp in the RNA-dependent polymerase region. Those teenagers with diarrhea were tested for Norovirus in their stool by RT-PCR. For those teenagers with cough, throat swabs were cultured for influenza and parainfluenza virus.

To reduce the risk for false-positive PCR results, we followed measures to avoid contamination during specimen handling and processing. Two primer sets were used for RT-PCR according to Ksiazek (4) and Drosten (5). The targets are located in the RNA-dependent RNA polymerase gene at different regions, which are separated by approximately 3,000 bp. The laboratory used in RT-PCR analysis is not involved in viral culture or extraction preparation and is located far away from the laboratory for RNA extraction to avoid contamination.

Negative-control cDNA was included in each analysis and confirmed that no contamination had occurred. Two operators manipulated RT-PCR analysis for two specimens from the same sample. The specimens were analyzed in different rooms with independent reagents for assurance. Real-time RT-PCR instead of nested RT-PCR was used.

Six schoolmates were positive for SARS-CoV by RT-PCR, confirmed later by DNA sequencing for replicase. The tested DNA sequence was >99% identical with a published SARS-CoV sequence. Norovirus was identified in one teenager's stool by RT-PCR; this virus belonged to genogroup I by testing partial cDNA sequence for capsid protein. The tested length was 555 bp, and the virus was 96% identical to strain KU4aGI. Culture of a throat swab for influenza and parainfluenza virus did not grow any virus.

The initial signs and symptoms of the nine teenagers were self-reported fever (9/9, range 37.8°C–39.4°C), cough (4/9), general malaise (4/9), diarrhea (4/9), rhinorrhea (3/9), headache (2/9), chills (2/9), sore throat (2/9), and myalgia (1/9). Cough

was productive in three schoolmates and dry in one. Chest x-ray results were normal for eight teenagers but showed linear interstitial pneumonia for one teenager. Four schoolmates took ribavirin for ≤2 days. Only the teenager with pneumonia was treated with both ribavirin and clarithromycin, for 12 days. The other four schoolmates did not take medication. All nine schoolmates became afebrile by the third day. Seven schoolmates were completely asymptomatic in 3 days. Two other schoolmates showed improvement and had normal values of all repeated laboratory tests in 5 days; however, they still had mild coughs on the seventh day, when they were discharged. The one teenager with interstitial pneumonia also had a normal chest x-ray result on the fifth day. All nine teenagers were discharged after 1 week of hospitalization and were continuously isolated in a special dormitory for another 2 weeks. No new cases of fever have occurred in Tzu-Chi High School in the 2 months since these patients' isolation.

Case-patient 2 was considered the index patient for SARS-CoV infection because of his travel history to Hong Kong. Six schoolmates with fever were confirmed by real-time RT-PCR and DNA sequences to have SARS-CoV infection. For students with diarrhea, only one case had coinfection with Norovirus. Influenza and parainfluenza viral infection was ruled out for students with cough. Because the nine ill schoolmates were isolated, no more cases of fever occurred in the school. All epidemiologic, molecular, and clinical studies showed evidence for SARS-CoV infection.

Worldwide, SARS-CoV infection has been clinically severe, characterized by respiratory distress and a 15% average mortality rate (6–8). Reported series of SARS with high mortality rates have involved mainly adults. Theoretically, subclinical or mild illness could be present and easily overlooked, and thus death rates could be overestimated.

The schoolmates in our series had mild illnesses and were identified only because of a special situation. On May 7, 2003, the World Health Organization (WHO) estimated that the case-fatality rate for SARS ranged from 0% to 50%, depending on the age group affected (8); for teenagers or younger children, the case-fatality ratio was <1%. Our teenagers with presumed SARS-CoV infection had very mild courses. This benign course was not related to treatment: only one teenager had a full course of ribavirin treatment, and most of the teenagers had either no specific medications or medications for <2 days. Our preliminary presumption for the benign course was the patients' young ages. The benign course of SARS-CoV infection in our teenage students supports the WHO finding of less-severe disease in younger persons. These reasons should be explored more fully and may facilitate the development of more effective treatment and prevention programs in persons of all ages.

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Conference Summary

SARS Preparedness and Response Planning

On July 5, 2003, less than 4 months after the first cases of severe acute respiratory syndrome (SARS) were recognized, the World Health Organization (WHO) declared that the global epidemic had been contained. Although the United States was not as severely affected by the SARS epidemic as parts of Asia and Canada, the outbreak response demonstrated both known and unexpected strengths and weaknesses in U.S. national, state, and local public health and healthcare capacities to address major infectious disease challenges. Although whether SARS will reappear is unknown, the public health and healthcare communities must be prepared for the possibility. As part of the preparedness and response planning process, the Centers for Disease Control and Prevention (CDC) convened a meeting August 12–13, 2003, in Atlanta.

The meeting had approximately 100 participants, including 30 external partners from international, national, state, and local agencies. The purpose of the meeting was to share experiences and lessons learned from the response to the SARS outbreak, describe anticipated needs in preparation for the possible reemergence of SARS, discuss SARS preparedness and response plans currently under development, and outline priority areas and roles of various partners in ensuring adequate preparedness at the national, state, and local level.

Two plenary sessions and a breakout session were held. The speakers in the first plenary outlined several key lessons learned during the outbreak response: 1) although some clinical features are suggestive of SARS, its symptoms overlap too much with those of other respiratory pathogens to make a clinical diagnosis; 2) risk of exposure is key to considering the likelihood of a diagnosis of SARS; 3) prompt use of isolation and infection control procedures was a key and effective part of SARS control; 4) quarantine was an integral part of SARS control in some settings with extensive transmission; and 5) testing multiple specimens (e.g., respiratory secretions, stool, and serum or plasma) may improve our ability to detect SARS-associated coronavirus (SARS-CoV) infection.

The speakers also described U.S. national, state, and local perspectives on SARS preparedness planning. They emphasized the need to integrate SARS preparedness planning with other preparedness efforts, such as those for pandemic influenza and bioterrorism, and to address legal, policy, and authority issues in responding to public health emergencies like SARS. The importance of international collaboration and cooperation in responding to an outbreak such as SARS and preparing for its possible return was also emphasized.

The speakers in the second plenary session highlighted the following lessons learned at the federal, provincial, and local levels during the SARS outbreak in Toronto, Canada: 1) public health units need flexible and robust surveillance and information technology systems to handle data-collection needs and facilitate rapid reporting of disease activity across and within multiple jurisdictions; 2) isolation and quarantine measures are acceptable if appropriately explained, but it is important to address issues of identification and tracking of contacts, to monitor potential contacts for noncompliance, and to provide them with social and economic support; 3) public health programs and hospitals require extensive expertise, resources, and good training to strengthen infection control practices; 4) laboratories should develop standard protocols and agreements regarding specimen and data sharing and ownership; and 5) accurate and timely dissemination of information are critical and should be tailored to the needs of specific groups, be easily accessible, and be culturally and linguistically appropriate.

Following the first plenary session, participants were divided into five workgroups to cover the following components of the SARS preparedness and response plans: 1) surveillance and information technology; 2) community preparedness and response (including isolation and quarantine); 3) healthcare preparedness; 4) laboratory; and 5) communications and education. Each workgroup was asked to define the key issues or needs for an effective response to SARS, preparedness activities that should be begun immediately, and the roles of federal, state, and local agencies and hospitals in these efforts. During the second plenary, each workgroup presented a summary of their discussions to the larger group of participants.

For surveillance, a flexible and functional response plan is needed that could be adapted to the various stages of a SARS epidemic and that integrates infection control activities both within hospitals and in the community. Key preparedness activities include educating healthcare workers about the diagnosis of SARS and developing guidelines for identification, reporting, and laboratory evaluation of potential SARS case-patients. Establishing an efficient data management system that links clinical, epidemiologic, and laboratory data and allows rapid sharing of critical and pertinent information was identified as a high priority.

For community response, guidelines should address issues of isolation and quarantine of SARS patients and their contacts, including consider-

ation of facilities for isolation (hospital, residential, other) and mechanisms of enforcement. The guidelines should be flexible and allow state or local officials to use their knowledge of local circumstances and judgment to determine which measures are most applicable. Successful implementation of containment measures will depend on public trust and require a consistent and clear communications plan. Groups that will be instrumental in implementing an effective response, such as the transportation industry, law enforcement, emergency services, and federal, state, and local legal experts, should be engaged early in the planning process. Training modules and drills that utilize realistic scenarios to evaluate the decision-making process and assess the feasibility of implementing containment measures should be developed, tested, and disseminated.

For healthcare preparedness, key considerations include defining infection control precautions for evaluating and handling patients with respiratory illness in the outpatient and inpatient setting, educating and training clinicians on clinical features of SARS and appropriate use of personal protective equipment, and building strong partnerships and collaborations between the clinical and public health communities, including cross-training staff in the areas of infection control and public health. Furthermore, issues of resource allocation and surge capacity in the event of a major SARS epidemic should be addressed.

For laboratory preparedness, guidelines should be updated for specimen collection, transport, and storage and the appropriate use of diagnostic tests and interpretation of test results. Surge capacity for testing at the federal, state, and local levels should be identified, and an adequate supply of reagents that have been properly validated and checked for quality should be ensured. While research to develop second-generation assays for improved diagnosis of SARS-CoV infection should continue, efforts should also focus on improving the performance of existing assays. Biosafety recommendations for specimen collection and laboratory processing must be updated. Guidelines for environmental testing for SARS-CoV must be developed and should include information on the role and utility of testing.

For communications and education, messages and curricula should be developed that target three audiences: public (including policy makers), physicians, and public health workers. Materials that were developed in response to the SARS outbreak must be reviewed and updated. Education and training efforts should focus on key areas, such as recognizing the clinical manifestations of SARS, appropriate use of infection control practices and personal protective equipment, rationale and practical guidance for implementing isolation and quarantine, and appropriate use and interpretation of laboratory diagnostic tests.

The information and ideas shared in this meeting are helping the public health and healthcare communities define priority SARS preparedness activities at the national, state, and local levels.

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Correction, Vol. 10, No. 1

In the article "*Bacillus anthracis* Incident, Kameido, Tokyo, 1993" by Hiroshi Takahashi, et al., errors occurred in the 4th paragraph under "Discussion" on page 119: mu symbols were inadvertently replaced by the letter "m." The corrected sentences appear below:

The human respiratory infectious dose 50 (dose that will produce an infection in 50% of exposed persons) is unknown but has been estimated to be 8,000 to 10,000 spore-bearing particles <5 µm in diameter (7). Kameido residents described a gelatinous substance, suggesting the suspension would be poorly dispersed and droplets would be too large to form particles <5 µm in diameter.

In addition, the name of the lead author of this article is misspelled in the table of contents of this issue. In the table of contents, the article should be attributed to "H. Takahashi et al."

The corrected article appears online at http://www.cdc.gov/ncidod/EID/vol10no1/03-0238.htm

We regret any confusion these errors may have caused.

Upcoming Infectious Disease Conferences

February 8–11, 2004
11th Conference on Retroviruses and Opportunistic Infections
Moscone West
San Francisco, CA
Contact: 703-535-6862
email: info@retroconference.org
Web site: www.retroconference.org

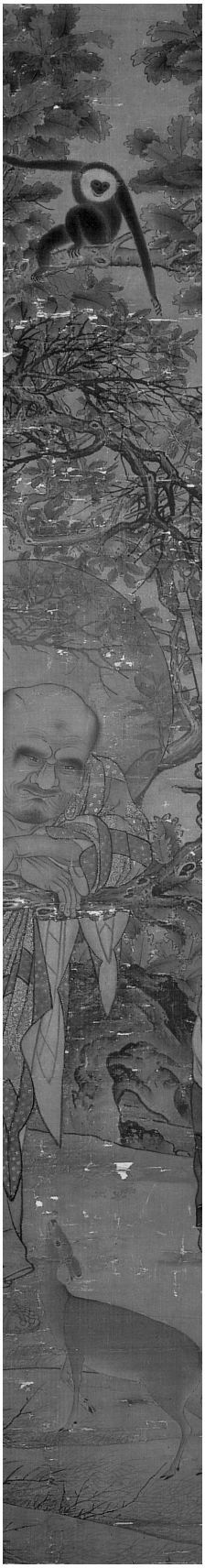
February 23–25, 2004
International Conference on Animal Welfare
Office International des Epizooties
Paris, France
Contact: 33 (0)1 44 15 18 88
email: oie@oie.int
Web site: www.oie.int

February 27–28, 2004
International Conference on Women and Infectious Diseases: From Science to Action
Atlanta Marriott Marquis
Atlanta, GA
Contact: BeJaye Roberts, 404-371-5492
Web site: http://www.womenshealthconf.org

February 28–March 3, 2004
International Conference on Emerging Infectious Diseases 2004
Atlanta, GA
email: iceid@asmusa.org
Web site: www.iceid.org

March 4–7, 2004
11th International Congress on Infectious Diseases
Cancun, Mexico
Contact: International Society for Infectious Diseases (617) 277-0551
email: info@isid.org
Web site: http://www.isid.org

April 13–16, 2004
International Conference on the Control of Infectious Animal Diseases by Vaccination
Office International des Epizooties
Buenos Aires, Argentina
Contact: 33 (0)1 44 15 18 88
email: oie@oie.int
Web site: www.oie.int



Liu Sung-nien (1174-1224), Sung Dynasty. Lohan (1207)

National Palace Museum, Taiwan, Republic of China. Hanging scroll, ink and colors on silk (117 cm x 55.8 cm)

Liu Sung-nien was a court painter from Ch'ien-t'ang (modern Hangchow). He painted figures and landscapes and was honored by Emperor Ning-tsung during the Sung Dynasty (960–1279), a prosperous and culturally rich period of Chinese history. The arts (silk tapestries, embroideries, calligraphy, lacquer, porcelain, pottery) explored the complexities of the physical and spiritual world, and painting reached full maturity in its reverence for nature and keen observation of life (1,2).

The Sung Dynasty embraced education and erudition and nurtured many cultural luminaries, who pondered the universe but walked among the people and had a down-to-earth accessible style. The lohans, Buddhist ascetics whose meditative personas inspired the pursuit of compassion and enlightenment, became a popular subject in paintings. Three of Liu's lohan works are in the National Palace Museum in Taiwan. The hanging scroll on this month's cover of Emerging Infectious Diseases is one of them.

In its entirety, the painting reflects harmonious human interaction with nature. The lightness of the scene, achieved through subtle brushstrokes and fluid, diaphanous earth hues, is punctuated by the playful presence of animals in an intimate ensemble, humans in the center, deer in the foreground, gibbons frolicking in the foliage above. The aged branches form a wrinkled halo around the lohan, who seems lost in thought. The cozy scene, intricately structured within an ancient pomegranate tree, embraces the sage and his acolyte in a warm give-and-take with the gibbons, while back-to-back, the deer gaze upward, one at the lohan, the other at the gibbons.

Elaborate detail is present throughout the scroll, including the upper part (cover selection) that crowns the pleasant scene. Yet, the creatures in the branches are abstract and stylized. The heart-shaped faces, characteristically long, tapering arms, and deep, humanlike eyes depict the essence but omit the details. Unlike the lohan, whose age and calling are dexterously outlined in his prominent visage, they are representational. On the periphery yet not to be ignored, they perform their acrobatic game with grace and confidence. They pick from the ancient tree and toss into the scene a pomegranate, thought by many to be the biblical fruit of knowledge (3).

Primates are common inhabitants of art scenes and feature frequently in Chinese literature. According to one legend, they, along with other animals, were once invited to a celebration held by the Jade Emperor of Heaven. Among the first 12 animals to arrive, monkeys were named part of the zodiac and were assigned a year on the Chinese solar/lunar calendar (4).

Liu's colorful scroll of nature nestled in the ancient pomegranate tree is a tempting metaphor for our times. The tart exotic fruit, its ageless perseverance within the leathery skin and its allusion to knowledge within the neatly membraned clusters of scarlet seeds, conveys optimism. The scene's moment of hilarity and harmony sends a message of community, where the answers to complex questions are collective and may well come from entirely unexpected places. While the lohan turns inward to think, the gibbon, like deus ex machina, passes the clue to the next of kin, who in turn will toss it over to those who have eyes to see.

Knowledge, a communal effort laboriously assembled piece by piece, relies on swift and purposeful give and take. Non-human primates more than once have held valuable clues to human puzzles, from AIDS to hepatitis. Sometimes the vehicle, but more often the oracle of zoonotic scourges, they have shared with us generously. In this the Chinese Year of the Monkey, the long arm of the gibbon may yet reach across the seas with seeds of knowledge for the global health community deciphering the puzzle of SARS.

Polyxeni Potter

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EMERGING INFECTIOUS DISEASES

A Peer-Reviewed Journal Tracking and Analyzing Disease Trends Vol.10, No.3, March, 2004

Upcoming Issue

For a complete list of articles included in the March issue, and for articles published online ahead of print publication, see http://www.cdc.gov/ncidod/eid/upcoming.htm

Look in the March issue for the following topics:

Clinical Trials and Novel Pathogens-Lessons from SARS

SARS Transmission and Hospital Containment

The RUsick2 Foodborne Disease Forum for Syndromic Surveillance

Reemerging Leptospirosis, California

Coronaviridae Features and SARS-associated Coronavirus Strain HSR1

Laboratory Analysis of Tularemia in Wild Trapped, Commercially Traded Prairie Dogs, Texas

Monkeypox Transmission and Pathogenesis in Prairie Dogs

Internet Use and Epidemiologic Investigation of Gastroenteritis Outbreak

Epidemiologic Trends and Genotypes of *Neisseria meningitidis* Causing Invasive Disease

Legionella Infection Risk from Domestic Hot Water

Acute Spotted Fever Rickettsiosis among Febrile Patients, Cameroon

Editorial Policy and Call for Articles

Emerging Infectious Diseases is a peer-reviewed journal established expressly to promote the recognition of new and reemerging infectious diseases around the world and improve the understanding of factors involved in disease emergence, prevention, and elimination.

The journal has an international scope and is intended for professionals in infectious diseases and related sciences. We welcome contributions from infectious disease specialists in academia, industry, clinical practice, and public health, as well as from specialists in economics, demography, sociology, and other disciplines. Inquiries about the suitability of proposed articles may be directed to the Editor at 404-371-5329 (tel), 404-371-5449 (fax), or eideditor@cdc.gov (e-mail).

Emerging Infectious Diseases is published in English and features the following types of articles: Perspectives, Synopses, Research Studies, Policy and Historical Reviews, Dispatches, Commentaries, Another Dimension, Letters, Book Reviews, and News and Notes. The purpose and requirements of each type of article are described in detail below. To expedite publication of information, we post journal articles on the Internet as soon as they are cleared and edited.

Chinese, French, and Spanish translations of some articles can be accessed through the journal's home page at http://www.cdc.gov/eid.

Instructions to Authors

Manuscript Preparation. For word processing, use MS Word. Begin each of the following sections on a new page and in this order: title page, keywords, abstract, text, acknowledgments, biographical sketch, references, tables, figure legends, appendixes, and figures. Each figure should be in a separate file.

Title Page. Give complete information about each author (i.e., full name, graduate degree(s), affiliation, and the name of the institution in which the work was done). Clearly identify the corresponding author and provide that author's mailing address (include phone number, fax number, and e-mail address). Include separate word counts for abstract and text.

Keywords. Include up to 10 keywords; use terms listed in Medical Subject Headings Index Medicus.

Text. Double-space everything, including the title page, abstract, references, tables, and figure legends. Printed manuscript should be single-sided, beginning with the title page. Indent paragraphs; leave no extra space between paragraphs. After a period, leave only one space before beginning the next sentence. Use 12-point Times New Roman font and format with ragged right margins (left align). Italicize (rather than underline) scientific names when needed.

Biographical Sketch. Include a short biographical sketch of the first author—both authors if only two. Include affiliations and the author's primary research interests.

References. Follow Uniform Requirements (www.icmje.org/index.html). Do not use endnotes for references. Place reference numbers in parentheses, not superscripts. Number citations in order of appearance (including in text, figures, and tables). Cite personal communications, unpublished data, and manuscripts in preparation or submitted for publication in parentheses in text. Consult List of Journals Indexed in Index Medicus for accepted journal abbreviations; if a journal is not listed, spell out the journal title. List the first six authors followed by "et al." Do not cite references in the abstract.

Tables and Figures. Create tables within MS Word's table tool. Do not format tables as columns or tabs. Send graphics in native, high-resolution (200 dpi minimum) .TIF (Tagged Image File), or .EPS (Encapsulated Postscript) format. Graphics should be in a separate electronic file from the text file. For graphic files, use Arial font. Convert Macintosh files into the suggested PC format. Figures, symbols, letters, and numbers should be large enough to remain legible when reduced. Place figure keys within the figure. For more information see EID Style Guide (http://www.cdc.gov/ncidod/EID/style_guide.htm).

Manuscript Submission. Include a cover letter indicating the proposed category of the article (e.g., Research, Dispatch) and verifying that the final manuscript has been seen and approved by all authors. To submit a manuscript, access Manuscript Central from the Emerging Infectious Diseases website (www.cdc.gov/eid).

Manuscript Types

Perspectives. Articles should be under 3,500 words and should include references, not to exceed 40. Use of subheadings in the main body of the text is recommended. Photographs and illustrations are encouraged. Provide a short abstract (150 words) and a brief biographical sketch of first author. Articles in this section should provide insightful analysis and commentary about new and reemerging infectious diseases and related issues. Perspectives may also address factors known to influence the emergence of diseases, including microbial adaptation and change, human demographics and behavior, technology and industry, economic development and land use, international travel and commerce, and the breakdown of public health measures. If detailed methods are included, a separate section on experimental procedures should immediately follow the body of the text.

Synopses. Articles should be under 3,500 words and should include references, not to exceed 40. Use of subheadings in the main body of the text is recommended. Photographs and illustrations are encouraged. Provide a short abstract (150 words) and a brief biographical sketch of first author—both authors if only two. This section comprises concise reviews of infectious diseases or closely related topics. Preference is given to reviews of new and emerging diseases; however, timely updates of other diseases or topics are also welcome. If detailed methods are included, a separate section on experimental procedures should immediately follow the body of the text.

Research Studies. Articles should be under 3,500 words and should include references, not to exceed 40. Use of subheadings in the main body of the text is recommended. Photographs and illustrations are encouraged. Provide a short abstract (150 words) and a brief biographical sketch of first author—both authors if only two. Report laboratory and epidemiologic results within a public health perspective. Although these reports may be written in the style of traditional research articles, they should explain the value of the research in public health terms and place the findings in a larger perspective (i.e., "Here is what we found, and here is what the findings mean").

Policy and Historical Reviews. Articles should be under 3,500 words and should include references, not to exceed 40. Use of subheadings in the main body of the text is recommended. Photographs and illustrations are encouraged. Provide a short abstract (150 words) and a brief biographical sketch. Articles in this section include public health policy or historical reports that are based on research and analysis of emerging disease issues.

Dispatches. Articles should be 1,000–1,500 words and need not be divided into sections. If subheadings are used, they should be general, e.g., "The Study" and "Conclusions." Provide a brief abstract (50 words); references (not to exceed 15); figures or illustrations (not to exceed two); and a brief biographical sketch of first author—both authors if only two. Dispatches are updates on infectious disease trends and research. The articles include descriptions of new methods for detecting, characterizing, or subtyping new or reemerging pathogens. Developments in antimicrobial drugs, vaccines, or infectious disease prevention or elimination programs are appropriate. Case reports are also welcome.

Commentaries. Thoughtful discussions (500–1,000 words) of current topics. Commentaries may contain references but should not include figures or tables.

Another Dimension. Thoughtful essays, short stories, or poems on philosophical issues related to science, medical practice, and human health. Topics may include science and the human condition, the unanticipated side of epidemic investigations, or how people perceive and cope with infection and illness. This section is intended to evoke compassion for human suffering and to expand the science reader's literary scope. Manuscripts are selected for publication as much for their content (the experiences they describe) as for their literary merit.

Letters. This section includes letters that present preliminary data or comment on published articles. Letters (500–1,000 words) should not be divided into sections, nor should they contain figures or tables. References (not more than 10) may be included.

Book Reviews. Short reviews (250–500 words) of recently published books on emerging disease issues are welcome. The name of the book, publisher, and number of pages should be included.

Announcements. We welcome brief announcements (50–150 words) of timely events of interest to our readers. (Announcements may be posted on the journal Web page only, depending on the event date.)

Conference Summaries. (500–1,000 words) of emerging infectious disease conferences may provide references to a full report of conference activities and should focus on the meeting's content rather than on individual conference participants.